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PRACTICE OF MEDICINE

VOLUME V

PRACTICE OF MEDICINE

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VOLUME V

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CONTENTS

VOLUME V

SECTION II: INFECTIOUS DISEASES (*Continued*)

CHAPTER PAGE

XL. RAT-BITE FEVER 1

By Henry Wolfer

Definition 1
Etiology 1
  Predisposing Causes 1
  Exciting Causes 2
Symptomatology 3
Clinical History 3
Physical Findings 4
Laboratory Findings 5
Diagnosis 5
Complications 5
Sequelæ 5
Clinical Varieties 5
Treatment 6
  Prophylaxis 6
  General Treatment 6
  Symptomatic Treatment 6
Prognosis 6
Pathology 6
Historical Summary and Distribution 7

XLI. ANTHRAX 9

By Samuel Sidney Woody

Definition 9
Etiology 9
  Predisposing Causes 9
  Exciting Causes 10
    Bacteriology 10
Symptomatology 11
Diagnosis 13
  Differential Diagnosis 14
Treatment 14
  Prophylaxis 14
  General Treatment 15
  Surgical Measures 16
  Serum Therapy 16

CHAPTER PAGE
Prognosis . . . 18
Pathology . . . 19
Historical Summary . . . 20

XLII. TETANUS . . . 25

By S. Potter Bartley

Definition . . . 25
Etiology . . . 25
  Predisposing Causes . . . 25
  Exciting Cause . . . 26
Symptomatology . . . 28
Clinical History . . . 28
Physical Findings . . . 30
Laboratory Findings . . . 30
Special Examinations . . . 31
Diagnosis . . . 31
Complications . . . 32
Clinical Varieties . . . 32
Treatment . . . 36
  Prophylaxis . . . 36
  General Management . . . 38
  Symptomatic Treatment . . . 38
  Surgical Treatment . . . 40
  Antitoxic Treatment . . . 40
  Phenol Treatment . . . 40
  Specific Serum (Antitoxic) . . . 40
Prognosis . . . 43
Pathology . . . 44
Statistical Summary . . . 45
Distribution . . . 46

XLIII. ROCKY MOUNTAIN SPOTTED FEVER . . . 49

By Lunsford D. Fricks

Definition . . . 49
Etiology . . . 49
  Mode of Transmission . . . 49
  Causative Agent . . . 50
  Prevalence . . . 52
  Seasonal Occurrence . . . 52
Symptomatology . . . 53
Diagnosis . . . 54
Treatment . . . 56
  Prophylaxis . . . 56
  Tick Eradication . . . 56
  General Measures . . . 57
  Serum Therapy . . . 58
Pathology . . . 58
Historical Summary . . . 59
Geographical Distribution . . . 60

XLIV. GLANDERS . . . 69

By Henry Wolfer

Definition . . . 69
Etiology . . . 69
  Predisposing Causes . . . 69

Exciting Cause 69
Symptomatology 72
Diagnosis 74
Treatment 75
Prophylaxis 75
General Management 75
Medicinal Treatment 76
Specific Therapy 76
Surgical Treatment 76
Prognosis 76
Pathology 76
Historical Summary and Distribution 77

XLV. HOOKWORM DISEASE 79

By C. C. Bass

Etiology 79
Predisposing Causes 79
Exciting Cause 81
Symptomatology 86
Clinical History 86
Physical Findings 90
Laboratory Findings 90
Diagnosis 92
Complications 93
Sequelæ 93
Association with Other Diseases 94
Treatment 94
General Prophylaxis 94
Individual Prophylaxis 95
Medicinal Treatment 95
Prognosis 98
Pathology 99
Historical Summary 102
Distribution 104
Sociological Aspect 105

XLVI. HODGKIN'S DISEASE 107

By Arthur F. Byfield

Definition 107
Historical Survey 107
Etiology 110
Predisposing Causes 110
Exciting Cause 111
Symptomatology 116
Diagnosis 131
Clinical Types 138
Treatment 141
Medicinal Treatment 141
X-ray and Radium Therapy 143
Surgical Treatment 144
General and Symptomatic Treatment 145
Prognosis 145
Pathological Anatomy 146

CHAPTER PAGE
XLVII. DISEASES DUE TO NEMATHELMINTHES 159

By Eugene R. Whitmore

Nematoda 159
  Nematodes in the Digestive Tract 160
    Ascariasis 160
    Oxyuriasis 168
    Ancylostomiasis 172
    Trichuriasis 173
    Trichiniasis 175
    Strongyloidiasis 187
  Nematodes in the Blood and Lymph 189
    Filariasis 190
    Other Filarial Infections 207
  Nematodes in the Subcutaneous Tissues 216
    Dracontiasis 216
  Nematodes in the Lungs 219
  Nematodes in the Kidneys 219
Acanthocephala 220
Gordiacea 220

XLVIII. DISEASES CAUSED BY ARTHROPODS 225

By Eugene R. Whitmore

Phylum: Arthropoda 226
  Class: Crustacea 226
  Class: Arachnidia 227
    Order: Pentostomida 227
      Porocephaliasis 227
    Order: Acarina 228
      Acariasis 228
    Order: Scorpionidea 239
    Order: Araneida 240
  Class: Myriapoda 241
  Class: Insecta 241
    Order: Hemiptera 242
      Suborder: Aptera 242
        Pediculosis 242
      Suborder: Heteroptera 244
    Order: Hymenoptera 247
    Order: Coleoptera 248
    Order: Lepidoptera 248
    Order: Orthoptera 249
    Order: Diptera 249
      Suborder: Aphaniptera 249
      Suborder: Brachycera 254
      Suborder: Nematocera 268

XLIX. INFLUENZA 275

By Hugo A. Freund

Introduction 275
Definition 276
Etiology 276
Bacteriology 279
Immunity 283
Symptomatology 286

CHAPTER PAGE
Incubation 286
Laboratory Findings 296
Convalescence 297
Complications 298
Treatment 305
Treatment of Symptoms 305
Serum Therapy 308
Pathology 309
Historical Summary 314
Bibliography 325

L. ACUTE POLIOMYELITIS 335

By Harold L. Amoss

Definition 335
Etiology 336
Pathology 339
Symptomatology 343
Diagnosis 348
Differential Diagnosis 349
Treatment 350
Serum Treatment 350
General Treatment 352
Treatment of Paralyses 352
Prevention 352
Carriers 356
Prognosis 358
Historical 358

LI. TUBERCULOSIS OF THE GENITO URINARY SYSTEM 361

By Anton G. Rytina

Introduction 361
Etiology 362
Tuberculosis of Kidney and Ureter 364
Chronic Tuberculosis of Kidney 374
Papillary Tuberculosis of Kidney 375
Tuberculous Pyonephrosis 375
Auto-Nephrectomy 375
Tuberculosis of the Bladder 376
Genital Tuberculosis 381
Tuberculosis of the Prostate 383
Tuberculosis of the Seminal Vesicles 383
Tuberculosis of the Testicle and Epididymis 384
Tuberculosis of the Urethra 387
Tuberculosis of the Glans Penis 387
Bibliography 388

LII. BRONCHOPNEUMONIA 391

By Arthur L. Bloomfield

Synonyms 391
Definition 391
Etiology 392
Symptomatology 396
Diagnosis 403

CHAPTER PAGE

- Complications and Sequelæ 403
- Treatment 404
  - Vaccine 405
  - General Treatment 405
  - Symptomatic Treatment 409
  - Specific Therapy 412
  - Treatment of Complications 413
  - Convalescence 415
- Prognosis 415
- Pathology 415

LIII. PYOGENIC INFECTIONS 421

BY MAX MINOR PEET

- Introduction 421
- Streptococcus Septicemia 422
  - Definition 422
  - Complications 428
  - Association with Other Diseases 428
  - Treatment 429
  - Prognosis 431
  - Pathology 431
- Staphylococcus Septicemia 433
  - Definition 433
  - Etiology 433
  - Symptomatology 434
  - Diagnosis 436
  - Treatment 437
  - Prognosis 438
  - Pathology 438
- Colon Bacillus Septicemia 439
  - Etiology 439
  - Symptomatology 440
  - Diagnosis 441
  - Complications and Sequelæ 442
  - Treatment 442
  - Prognosis 442
  - Pathology 442
- Bacillus Pyocyaneus Septicemia 443
  - Definition 443
  - Etiology 443
  - Diagnosis and Symptomatology 447
  - Complications 448
  - Sequelæ 449
  - Association with Other Diseases 449
  - Clinical Varieties 450
  - Treatment 450
  - Prognosis 451
  - Pathology 451
  - Historical Summary 452
- Bacillus Mucosus Capsulatus Septicemia 452
- Micrococcus Tetragenous Septicemia 453
- Meningococcus Septicemia 453
- Pneumococcus Septicemia 453
- Gonococcus Septicemia 454
- Bibliography 454

CHAPTER PAGE
LIV. GLANDULAR FEVER 457

By Walter F. Watton

Definition 457
Etiology 457
Symptomatology 458
Diagnosis 459
Complications 459
Treatment 459
Prognosis 460
Pathology 460
Bibliography 460

LV. APHTHOUS FEVER 461

By Walter F. Watton

Definition 461
Etiology 461
Symptomatology 461
Diagnosis 462
Treatment 462
Prognosis 462

LVI. WHOOPING COUGH 463

By Mansfield G. Levy

Definition 463
Etiology 463
    Exciting Causes 464
    Infective Period 464
    Incubation 464
Symptomatology 464
    Catarrhal Stage 464
    Spasmodic Stage 464
    Stage of Decline 465
    General Features 465
Diagnosis 465
Complications 466
Treatment 466
    Prophylaxis 466
    General Management 467
Prognosis 468
Pathology 468

LVII. TAPEWORMS AND FLUKES 471

By Norman B. Cole

Cestodes 471
    Tænia saginata 473
    Tænia solium 473
    Tænia confusa 474
    Tænia echinococcus 474
    Echinococcus multilocularis 476
    Hymenolepis nana 476
    Hymenolepis diminuta 477
    Dibothriocephalus latus 477
    Diplogonoporus grandis 477
    Dipylidium canium 478

CHAPTER PAGE
Davainea madagascariensis 478
Sparganum mansoni 478
Sparganum proliferum 478
Trematodes 479
Hepatic distomiasis 479a
Clonorchis sinensis 479a
Fasciola hepatica 479b
Opisthorcis felineus 479b
Dicrocœlium lanceatum 479b
Pulmonary distomiasis 479c
Venal distomiasis 479c
Schistosoma hematobium 479c
Schistosoma mansoni 479d
Schistosoma japonicum 479d
Intestinal distomiasis 480

SECTION III: DISEASES OF THE RESPIRATORY SYSTEM

I. ALLERGIC CORYZA 481

By Robert A. Cooke

Introduction 481
Etiology 482
Symptomatology 483
Clinical History 483
Diagnosis 485
Differential Diagnosis 485
Complications 486
Association with Other Diseases 486
Clinical Varieties 486
Treatment 487
General Measures 487
Climatic Treatment 488
Prognosis 489
Pathology 490
Historical Summary 490

II. BRONCHIAL ASTHMA 493

By Robert A. Cooke

Definition 493
Etiology 493
Symptomatology 499
Clinical History 499
Diagnosis 507
Differential Diagnosis 508
Complications 509
Clinical Varieties 509
Treatment 513
Symptomatic Treatment 513
Medicinal Treatment 513
Inhalants 513
General Measures 514
Specific Treatment 514
Prognosis 516
Pathology 516

CHAPTER PAGE
III. DISEASES OF THE LUNGS 519

By Louis Francis Jermain

Congestion of the Lungs 519
Pulmonary Edema 524
Hemoptysis 527
Embolism, Thrombosis and Infarction of the Lung 531
Cirrhosis of the Lungs 534
Pneumonoconiosis 541
Emphysema of the Lungs 544
Pulmonary Abscess and Gangrene 554
Tumors of the Lung 565

IV. DISEASES OF THE PLEURA 577

By Charles P. Emerson

Acute Inflammatory Diseases of the Pleura and Their Sequelæ . 578
Classification 578
  Acute Fibrinous Pleurisy, Plastic Pleurisy and Dry Pleurisy . 579
  Serofibrinous Pleurisy, Pleurisy with Effusion 593
  Empyema 615
  Hemorrhagic Pleurisy 630
Noninflammatory Exudates Within the Pleura 631
  Pneumothorax 631
  Hydrothorax 647
  Hemothorax 649
  Chylothorax 649
Pleuromycoses 650
  Actinomycosis of the Pleura 650
  Nocardiosis of the Pleura 651
Tumors of the Pleura 652
  Carcinoma of the Pleura 652
  Primary Sarcoma of the Pleura 653
  Secondary Malignant Tumors 653
Echinococcus Diseases of the Pleura 654

V. DISEASES OF THE BRONCHI 659

By Luther F. Warren

Bronchitis 659
  Definition 659
  Etiology 659
Acute Bronchitis 660
  Influenzal Bronchitis 661
  Capillary Bronchitis 662
Chronic Bronchitis 674
  Bronchitis and Heart Disease 678
  Bronchitis and Renal Disease 679
  War Bronchitis 679
  Dry Bronchitis of Laennac 680
  Serous Bronchitis of Laennac 680
  Purulent Bronchitis 680
Plastic Bronchitis 683
Putrid Bronchitis 690
Tracheobronchial Syphilis 692
New Growths of the Bronchi 698

LIST OF ILLUSTRATIONS

VOLUME V

SECTION II: INFECTIOUS DISEASES (*Continued*)

CHAPTER XLIII

ROCKY MOUNTAIN SPOTTED FEVER

Colored Plate

PLATE PAGE
I. Rocky Mountain Spotted Fever, showing full developed eruption . *Facing* 54
FIGURE
1. Typical chart of severe human case of Rocky Mountain Spotted Fever 55
2. Distribution of Rocky Mountain Spotted Fever in the United States 61

CHAPTER XLV

HOOKWORM DISEASE

1. Necator Americanus 83
2. Section of skin as seen under the microscope, showing the hookworm larvæ crawling through the skin. (After Stiles.) 84
3. Photograph showing dwarfing effect of the disease 89
4. Preparation made by Bass method from feces 92
5. Photomicrograph of Uncinaria Americana Sucking Mucosa . . . 101

CHAPTER XLVI

HODGKIN'S DISEASE

1–4. Hodgkin's Disease. Cervical Tumors Predominatingly Left-sided (Fig. 1), Right-sided (Fig. 2), Bilateral in the Lower Half of the Neck (Fig. 3), and in the Upper Half (Fig. 4). (From Kurt Ziegler, Die Hodgkinsche Krankheit, Jena, 1911) 117
5. Hodgkin's Disease—Generalized Form. A Case Observed by the Author with Dr. Charles A. Elliott. Photograph Kindly Loaned by Dr. Elliott 119
6. Hodgkin's Disease. Lymph-node 148
7. Hodgkin's Disease. A Higher Magnification of a Portion of Figure 6 149
8. Hodgkin's Disease. A Section of Lymph-node Illustrative of Well-advanced Changes. To a Great Extent Hyalin Connective Tissue

PRACTICE OF MEDICINE

VOLUME V

SECTION II

INFECTIOUS DISEASES (*Continued*)

CHAPTER XL

RAT-BITE FEVER

By Henry Wolfer, M. D.

Definition, p. 1—Etiology, p. 1:—Predisposing causes, p. 1; Exciting causes, p. 2—Symptomatology, p. 3:—Clinical history, p. 3; Physical findings, p. 4; Laboratory findings, p. 5—Diagnosis, p. 5—Complications, p. 5—Sequelæ, p. 5—Clinical varieties, p. 5—Treatment, p. 6:—Prophylaxis, p. 6; General treatment, p. 6; Symptomatic treatment, p. 6—Prognosis, p. 6—Pathology, p. 6—Historical summary and distribution, p. 7.

Definition.—Rat-bite fever is an infectious disease following the bite of a rat, less commonly the bite of a weasel, ferret, cat or squirrel, and is characterized by paroxysms of fever followed by periods of remission, by a local inflammatory reaction about the bite wound with contiguous lymphatic glandular enlargement, and by a bluish-red macular exanthem.

Etiology.—PREDISPOSING CAUSES.—The development of the disease follows the bite of the animal, usually a rat, which transmits the infective organism to humans. It is of infrequent occurrence, except in Japan, where the manner of housing the people accounts in part for the prevalence in that country. Cases have been reported from various sections of the United States, from many of the European countries, and recently from the tropics, showing a wide distribution, *uninfluenced by regional or climatic conditions. Age* and *sex* are *not influencing factors.*

Alcoholism, exposure, mental and physical *overwork,* undoubtedly influence this, as other infections, only by lowering the general body resistance, and *not as direct predisposing causes.*

Individual susceptibility varies. There is evidence that some individuals possess a natural immunity. In the literature, cases are cited in which two persons were bitten by the same rat but only one developed the disease. Or in other cases, both became infected, one showing a more severe type than the other.

Bite wounds on the exposed parts of the body, as in hydrophobia, are most apt to be followed by the disease. It is said that puncture wounds with little bleeding are the most dangerous, and that head and neck bites have a shorter period of incubation; but the mere location of the wound does not determine the subsequent development or severity of the infection.

Exciting Causes.—Since Ogata, in 1908, discovered the *Sporozoa muris* (which he now believes to be an Aspergillus) in the blood, lymph-glands, and bite-wound in cases of rat-bite fever, various organisms have been described as etiological agents. Middleton, in his case, reports the finding of a diplococcus, Proescher, of a small, poorly-staining bacillus, Ofenheim, of a *Micrococcus tetragenus*, and recently Douglas, and others, of a streptococcus of the pyogenic group. In Germany, Schottmüller (1914) obtained a streptothrix, which he called the *Streptothrix muris ratti*, in eight successive blood cultures, during a period of two months. Blake, in this country, confirmed the association of the streptothrix in his case report, and Tileston was also able to demonstrate its presence in one of two cases.

The *Streptothrix muris ratti* is a thread-like branching organism, the filaments varying in length, being either straight or curved in form. It is a facultative anaërobe, capable of artificial growth, and shows a tendency to fragmentation and formation of terminal, oval, and ball-shaped swellings. The fragmentation assumes bacilli- and cocci-like forms. It takes the common stains readily and is gram-negative.

In Blake's case, which was followed to autopsy, the organism was only obtained from the circulating blood and from the mitral valves, which showed an acute ulcerative endocarditis. Animal inoculations, aside from producing local inflammatory lesions at the site of inoculation, have not proven successful.

The Japanese physicians have contributed greatly to our knowledge of rat-bite fever, and in 1916 Futaki and his co-workers reported the finding of a spirochete in 2 cases of the disease, and again in 5 later cases the same organism, which he calls the *Spirochæta morsus muris*, was found. All the cases were of Japanese origin. The organism was obtained from the circulating blood, lymph-glands, and in a section of skin showing the characteristic eruption of the disease. These findings have since been confirmed by Kaneko and other Japanese physicians.

The *Spirochæta morsus muris* is believed to belong to the protozoan group of organisms. It varies in size from one and a half to twelve microns and shows from two to six regular or irregular curves. In some the tapering ends form flagella. Two forms have been described, one showing a short, thick body, the other, a long, thin body; both of these are believed to be modifications of the same organism. The structural differences are believed to be due to animal inoculations, or simply different stages in its development. It can be cultivated by Noguchi's and Shimamine's method; it stains readily with Giemsa's stain and in the tissues by Levaditi's silver impregnation method. It is also readily demonstrated by Burri's India ink method and by the dark field illumination.

The *Spirochæta morsus muris* has been found in the area of skin showing the eruption, in lymph-glands, at the site of the bite, and in the circulating blood during the paroxysms of fever. In the apyrexial periods the number in the blood is reduced and difficult to estimate. The most common sites of the organism in the internal organs are the kidneys, the cortex of the adrenals and the testicles.

Y. Ito and others have shown that the blood of patients recovering from rat-bite fever possesses spirochetalytic and spirocheticidal bodies of rather weak but specific nature for the *Spirochæta morsus muris.*

Animal inoculations with the blood from patients suffering with the disease have been successful in infecting monkeys, rats and guinea pigs, and from these other animals have been successfully infected. The same general distribution of the spirochete has been observed in the body of animals as in the fatal case reported by Kaneko. It is interesting to note that the organism was found in 3 per cent. of the common brown rats and in the salivary glands of white rats experimentally infected. It is undoubtedly through the saliva that the spirochete is conveyed.

Certain features of rat-bite fever, such as the long period of incubation, the glandular enlargement, the rash, the paroxysms of fever of a remittent type and its response to treatment, favor the idea that the disease is of the spirochetal variety. This, with the recent work of Japanese physicians, is sufficient evidence that the *Spirochæta morsus muris* is the cause of rat-bite fever as it exists in Japan. It is possible that the other organisms described are secondary or accidental invaders; or we must assume they are capable of producing a similar clinical syndrome. Until further confirmatory evidence is added to our knowledge of the causative organism or organisms the question must be held in abeyance.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The incubation period of the disease is usually from ten to twenty-seven days. It may vary from a few days to several months, the average time being two weeks.

Prodromal Symptoms.—The majority of cases show no prodromal symptoms. A day or two previous to the onset, such slight, indefinite symptoms as headache, vague muscular pains, and general malaise may be present.

Mode of Onset.—With the onset of the disease, the site of the bite, which has healed without showing any evidence of an infectious character, becomes painful, swollen, and of a bluish-red color. Signs of lymphangitis may be seen leading to the neighboring group of lymphatic glands, which become enlarged and tender. This local reaction is quickly followed by a chill, or chilly sensations, and by a rapid rise of temperature to from 103° to 105° F. (39.4° to 40.5° C.).

Course of Disease.—The patient now complains of severe muscular pain and tenderness, especially in the lower extremities, and this constitutes one of the characteristic symptoms of the disease. Headache, dysphagia, weakness, anorexia, and joint pains appear. Nausea, vomiting and vertigo may also be present. Prostration appears early and is marked, and in severe cases pronounced mental symptoms, as delirium and hallucinations, develop. In the majority of cases the characteristic rash appears during the first febrile attacks, and may be limited to the area about the wound; more often it is general in its distribution. It consists of bluish red, slightly raised macules, with sharply-defined margins, which vary from 1 to 10 cm. in diameter. The temperature, which at times shows considerable daily variation, persists from three to five days, and then drops to normal by crisis accompanied by a profuse perspiration. With the fall in temperature the constitutional and local symptoms subside. There is now a period of apyrexia of from four to six days, during which the patient feels fairly comfortable, and then a second paroxysm takes place. The rash, which had faded, reappears; the lymph-glands again become enlarged and painful, and with the fever the constitutional symptoms return. The pyrexial attacks continue to assume a relapsing type, so that each week usually shows one paroxysm. In favorable cases, as the disease progresses the relapses appear at longer intervals, are of shorter duration, and are accompanied by slight general symptoms, finally terminating in an abortive afebrile attack. Rapid emaciation and cachexia are often prominent features as the disease progresses, and in addition to the nervous symptoms before mentioned, motor and sensory disturbances may appear. These affect chiefly the lower extremities, and in addition to paresthesia and anesthesia there is marked muscular weakness with diminished or absent tendon reflexes. Occasionally the patellar reflex is exaggerated.

The duration of the disease is usually from one to three months. According to Kusunoki, annual or biennial relapses occur for ten years after recovery from rat-bite fever, and a case has been known in which the patient suffered from recurrences fifteen years after the initial attack. Mild cases may present only one or two paroxysms with minor constitutional disturbances, while in severe types the temperature may continue without remissions, and be marked by delirium and stupor; the patient finally passes into a comatose condition and dies.

The reaction of the wound may be lacking or show only slight inflammatory changes, while at other times the severity may be so great that circumscribed areas of necrosis are formed. Vesicles may develop about the swollen area. Suppuration about the wound indicates the presence of a secondary infection. In addition to the typical macules an erythema may be present, and patches are often located in the neighborhood of the involved glands. An acute urticaria may make its appearance late in the disease and disappear as the temperature subsides.

Physical Findings.—The physical examination, except for the local manifestations, rash, and glandular enlargement, demonstrates no important findings. Lymphatic glandular enlargement may be found in various groups, but not to the extent of those proximal to the bite wound. The heart may show the presence of functional murmurs due to the anemia and emaciation. Signs of a slight bronchitis may occasionally appear. A valuable negative finding is the absence of splenic enlargement. The tendon reflexes are modified or absent in cases showing the sensory motor features.

Laboratory Findings.—Examination of the blood reveals a leukocytosis of from fifteen to twenty thousand with a relative increase in the polymorphonuclear neutrophils, and at times a slight increase in the eosinophils. During the apyrexial periods the count returns to normal. A marked secondary anemia is produced as the disease progresses. The blood Wassermann reaction, as in other spirochetal diseases, may be found positive, and is therefore of no value in determining the coexistence of a syphilitic infection. The urine shows the usual febrile characteristics during the paroxysms. Later the toxic action of the infection on the renal epithelium produces large amounts of albumin and many hyalin and granular casts.

Diagnosis.—Rat-bite fever may be confused with *erysipelas, septic infection, malaria, syphilis,* and *relapsing fever.* Attention to the following features will aid in arriving at a diagnosis: the history of a rat-bite; the local inflammatory reaction and bluish-red macular eruption; recurring paroxysms of fever of a remittent type; and the severe general muscular pains and tenderness.

Leukocytosis present only during the pyrexial periods, and the absence of splenic enlargement, are valuable aids.

Complications.—The principal complications are *nephritis* and a profound *asthenia. Cardiac paralysis* has been observed in 1 case.

Sequelæ.—Convalescence is prolonged, the patient complaining of general weakness long after the attack. Neuralgic pains in various parts of the body may be a troublesome sequela.

Clinical Varieties.—The Japanese physicians have classified the disease into three and four types, depending upon the predominating local manifestations, the course of the temperature, and the presence of marked nervous symptoms.

Crohn, in his excellent description of the disease, mentions the following types:

I. Afebrile type with only subjective symptoms, and mild in character.

II. Type showing continuous temperature, which may be severe, with marked nervous symptoms, and prove rapidly fatal, or mild and abortive with slight constitutional symptoms.

III. The intermittent type, showing the recurring pyrexial attacks, the inflammatory reaction, and the characteristic bluish-red eruption.

IV. Miscellaneous types: Cases not classified above, and which may show the local symptoms predominating, the incubation period short or absent, or other changes from the usual type.

Treatment.—PROPHYLAXIS.—The principal prophylactic measures should be directed toward the prompt treatment of the bite wound. As soon after the occurrence of the bite as is possible the wound should be **cauterized** with pure **phenol,** and a wet dressing of a **bichlorid of mercury solution,** 1-3,000, applied. The actual cautery and the injection of a 5 per cent. phenol solution about the bite wound is recommended by Miyake.

GENERAL TREATMENT.—Hata in 1912 published his results with the use of **arsphenamin** (salvarsan) in 8 cases of the disease. He was able to effect a cure in 5 cases. A single injection was given to each patient. Subsequent reports of the use of this remedy have proven its value. A single injection of 0.3 gram (4.63 grains) given in the same manner as for syphilis is curative in the majority of cases. A second and third injection may be given in those cases which show relapses. Of 12 cases reported as receiving arsphenamin, 10 recovered. The newest preparations, as neo-arsphenamin, in a corresponding dosage, may be employed. The remedy, which acts like a specific medication, may be given during the pyrexial attacks.

SYMPTOMATIC TREATMENT.—Other treatment of the disease is along purely symptomatic lines. **Codein, aspirin, antipyrin,** or **acetphenetidin,** etc., may be given to relieve the severe muscular pains, and during convalescence some preparation of iron with **strychnin,** and a **bitter tonic** may be employed for the anemia and general weakness.

Prognosis.—In fatal cases of the disease the patient dies in a comatose condition or from gradual asthenia. Nephritis may prove to be a fatal complication. The mortality of rat-bite fever is given as 10 per cent., but the recent introduction of arsphenamin into the treatment, with such brilliant results, will undoubtedly greatly reduce this figure and shorten or prevent the long convalescence. Unfavorable features during the course of the disease are the continued high temperature, with severe cerebral symptoms, marked emaciation, cachexia, and the development of nephritis.

Pathology.—Until the recent reports by Blake and Kaneko, describing the gross and microscopical findings in their cases of the disease, our knowledge of the changes produced was very meager. In the only other autopsy report, by Miura in 1897, no marked anatomical changes were found and no histological studies made. It will be recalled that Blake found *Streptothrix muris ratti,* and that Kaneko confirmed the presence of the *Spirochæta morsus muris* as the causative organism. As the autopsy observations were also at variance, a description of both cases will be given.

In Blake's case, the principal anatomical finding was an acute ulcerating endocarditis affecting the mitral valve, the blood infection by the streptothrix apparently localizing itself in that site. The lungs showed moderate, and the liver marked, passive congestion. Two areas of infarction were present in the spleen, which was soft and edematous. The kidneys were small and without definite markings. The gastrointestinal tract, pancreas, bladder, adrenals, and brain appeared normal.

The principal microscopical findings described were a subacute myocarditis with cellular infiltration and new tissue formation taking place of the heart-muscle (in the necrotic areas at the periphery of the valve, masses of long slender bacilli-like organisms were seen); subacute interstitial hepatitis also showing cellular infiltration and areas of atrophic liver-cells; subacute glomerular and interstitial nephritis, the capillaries of the glomerules being thickened and sclerotic, the interstitial process showing acute and healed stages; perivascular exudation in the adrenals; and infarcts of the spleen and kidney.

In the case of Japanese origin reported by Kaneko, no distinctive pathological findings were noted. The chief changes were of a parenchymatous nature in the heart, kidneys, and liver. The axillary glands on the involved side and those of the mesentery were moderately enlarged. Changes of a mild catarrhal character were seen in the mucosa of the stomach, intestines, and urinary bladder. The lungs, pancreas, adrenals, meninges, and brain showed hyperemic changes.

Of the histological changes the most pronounced were found in the renal cells of the convoluted tubules, which contained numerous hyalin casts. The condition of the cells varied from a cloudy swelling to fatty degeneration and necrosis. The liver-cells of the acini centers showed similar fatty and necrotic changes, while in the peripheral cells the degenerative changes were less marked. Other milder degenerative changes were seen in the cells of the adrenal cortex, muscles, brain, and cord. There was present in the axillary glands changes of a simple inflammatory character, with hyperplasia of the adenoid tissue and evidences of slight erythrophagocytosis.

Historical Summary and Distribution.—The Japanese physicians were familiar with the manifestations of rat-bite fever for many years prior to the publication of an article by Miyake (1900) which brought the disease to the attention of European physicians as a definite clinical entity. In Japan the disease is known as "Sodoku," and the fact that severe constitutional symptoms often followed a rat-bite was known to the laity. Japanese literature contains many early reports and excellent descriptions of the disease. In European literature only 2 cases of rat-bite followed by clinical symptoms are found previous to Miyake's article. Since then, particularly during the past few years, numerous cases have been reported in the British literature, and less frequently in France, Spain, Italy, and Germany. The first American report of a case following a rat-bite was made by Wilcox in 1840; recently Proescher, Crohn, Blake, Tileston, Brenneran, and Gundrumn have reported cases occurring in widely separated sections of the country. As cases of the disease have also been reported from India and Australia its distribution may be said to be almost worldwide.

BIBLIOGRAPHY

Atkinson, A. C. Med. Chron., Manchester, 1912-13, Series 4, lvii, 1.
Blake, F. G. Jour. Exper. Med., 1916, xxiii, 39.

Brenneran, F. F. Surg. Clin., Chicago, 1918, ii, 488.
Crohn, B. B. Archiv. Int. Med., 1915, xv, 1014.
Dalal, A. K. Practitioner, London, 1914, xcii, 449.
Douglas, S. R., *et al.* Lancet, 1918, i, 253.
Futaki, K., *et al.* Jour. Exper. Med., 1917, xxv, 33.
——— *Idem.* Jour. Exper. Med., 1916, xxiii, 249.
Gundrumn, F. F. Calif. State Jour. Med., 1918, xvi, 16.
Hata, S. München. med. Wchnschr., 1912, lix, 854.
Horder, T. J. Quart. Jour. Med., 1909-1910, iii, 121.
Ishwara, K., *et al.* Jour. Exper. Med., 1917, xxv, 45.
Ito, Y., *et al.* Jour. Exper Med., 1917, iii, 377.
Kaneko and Okuda. Jour. Exper. Med., 1917 iii, 363.
Kitagawa, J. Arch. Int. Med., 1917, xx, 317.
Middleton, G. S. Lancet, 1910, i, 1618.
Miyake, H. Mitt. a.d. Grenzgeb. d. Med. u. Chir., 1900, v, 231.
Nixon, J. H. Brit. Med. Jour., 1914, ii, 626.
Ogata. Mitt. a.d. Med. Fakult. d.k. Univ. z. Tokyo, 1909, viii, 287.
Proescher, F. Internat. Clinics, 1911, Series 21, iv, 77.
Schottmüller, H. Dermat. Wchnschr., 1914, lviii, Supp. 77.
Surveyor, N. F. Lancet, 1913, ii, 1764.
Tileston, J. Jour. Am. Med. Assn., 1916, lxvi, 995.
Wilcox, W. Am. Jour. Med. Sc., 1840, xxvi, 245.

CHAPTER XLI

ANTHRAX

BY SAMUEL SIDNEY WOODY, M.D.

Definition, p. 9—Etiology, p. 9:—Predisposing causes, p. 9; Exciting cause, p. 10:—Bacteriology, p. 10—Symptomatology, p. 11—Diagnosis, p. 13:—Differential diagnosis, p. 14:—Treatment, p. 14:—Prophylaxis, p. 14; General treatment, p. 15; Surgical measures, p. 16; Serum therapy, p. 16—Prognosis, p. 18—Pathology, p. 19—Historical summary, p. 20.

Definition.—Anthrax, or malignant pustule, is an acute, specific, virulent, infectious disease occurring among animals, mainly cattle, sheep and horses. It is never spontaneous in man but is communicable from animals, either by contact or by inhalation or ingestion of the specific organism from infected animals or animal material.

Etiology.—PREDISPOSING CAUSES.—It is prevalent in *all parts of the world*, but is less common in the United States than in Europe and Asia, where it often occurs in epidemic form and is most fatal during the warm summer months. It seems to favor those countries where the *soil is marshy* or the sub-soil is tenacious or impermeable, as in certain parts of Germany and the countries along the Danube. In Russia and China it is especially virulent, large numbers of horses dying of the disease annually in those countries; in Asia Minor it attacks the Angora goat which provides so much of the commercial wool and mohair. Besides horses, sheep and cattle, other animals that are susceptible to anthrax are swine, goats, rabbits, guinea pigs, mice, foxes, less often dogs, cats, fowl and birds. In animals the disease is acquired principally through forage in pastures.

According to the figures of the United States Bureau of Labor Statistics, the greater number of cases of human anthrax in this country are reported during the late winter and early spring months, but as yet there is no way of telling whether or not this *seasonal* incidence is anything more than a matter of chance. As to *sex*, it is but natural that the disease should be more prevalent among males, inasmuch as male workers predominate in the industries that carry with them the menace of anthrax. This applies also to *age*. The greatest number of cases and fatalities occur during the working age of life; otherwise the disease respects neither the young nor the old. It has been reported in an infant of one month who was accidentally bitten by a dog that had come in contact with the cadaver of an infected animal. Old people are subject to similar or other modes of infection.

In *man* the disease is mainly an *occupational* one, affecting woolsorters, tanners, brush-makers, workers on mattresses, and others who handle the carcasses of the raw material of animals that have died of anthrax. Occasionally it attacks laboratory workers, and not infrequently it results from the use of improperly prepared furs, false hair, and shaving brushes. The rôle of the shaving brush as a source of infection has been emphasized during the war years in the military training camps, the disease thus contracted having proved fatal in a number of instances. Attempts to disinfect the brushes before distributing them among the men proved useless, since a solution that was effective in destroying the germ also destroyed the brush. It is therefore the question of the proper preparation of the bristles at the factory which should receive the attention of public health authorities, while the public should be warned to use only such brushes as bear the stamp of a reliable firm.

Exciting Cause.—*Bacteriology.*—*Bacillus anthracis* is a slender nonmotile rod of varying length. Sometimes several rods are joined in threads or chains, the free ends being slightly rounded while the contiguous ones are angular. The bacillus is enclosed in a transparent envelop which takes on a lighter stain than the rod it surrounds. Under favorable conditions it develops oval spores which are gradually set free from the mother-cell. Spore-formation, however, is often irregular and sometimes entirely wanting.

The sporeless variety rapidly loses its vitality, but the spore-bearing bacillus is noted for its tenacity of life, especially when grown in rich albuminous liquids. In dried anthrax blood it has been known to retain its virulence for as long as sixty days and in dried bouillon cultures for twenty-one days. The spores also retain their vitality for an indefinite time, and are very resistant to high temperatures. When exposed in dry air a temperature of 140° C. (60° F.) is necessary to destroy them, but when suspended in a liquid they are rapidly destroyed at 100° C. (37.78° F.).

In animals the organisms are distributed in large numbers in the blood, but they are less numerous in human blood. They are constantly found in and near the site of inoculation and in the neighboring lymphatic vessels; also in the vesicles about the local lesion and sometimes in the surrounding edematous area. In the late stages of the disease the bacillus can be recovered in blood from the ear or from the fingers, and in the urine when the kidneys are involved. It is also usually found—sometimes in large numbers—in sections from various tissues and organs.

Modes of Conveyance.—The specific organism, *Bacillus anthracis,* is excreted in the *urine and feces of affected animals* and the soil on which these are deposited, being a poor medium for the growth of the organism, develops spores which are very resistant to light, heat and other influences and therefore persist for an indefinite time.

The organism is also present in the *nasal and anal blood* flowing from dead or dying infected animals, which, providing a nutrient medium for the development of spores, thus offers additional opportunity for the spread of the infection by direct contact or through other animals, flies, insects, birds, etc. A field or soil thus infected is not easily freed of the anthrax bacillus. The organism is also apt to be deposited in pastures by means of *fertilizers* containing the waste from factories and tanneries. It is through tanneries also that the *water* enters into consideration as a factor in carrying infection in those localities where the streams or brooks from which animals at pasture are forced to drink have been contaminated.

Symptomatology.—Clinical History.—Human anthrax is generally characterized by an external lesion of the skin or mucous membrane, sometimes accompanied by a generalized blood infection and splenic enlargement; the symptoms may also be those of a septicemia without a visible external lesion.

Period of Incubation.—The incubation period cannot be determined with any degree of accuracy, since it can be estimated only from the appearance of the characteristic lesion, no prodromal symptoms or rash having been described. The period of incubation may vary from a few hours to as long as ten days.

In man the disease appears as external and internal anthrax, the former presenting two types, malignant pustule and malignant anthrax edema.

Mode of Onset.—Since the anthrax bacillus generally invades the body through a tiny abrasion of an exposed skin or mucous surface, it is in the form of *malignant pustule* that it is most frequently encountered, the favorite sites being the exposed parts, i.e., the neck, hands, arms, or the chest and shoulders if these are exposed while carrying wool, hides, or other infected animal material. In some instances it has been transmitted to other locations by scratching or rubbing the original sore, thus giving rise to multiple lesions.

The typical malignant pustule is a single lesion beginning with a slight itching or burning sensation accompanied by a reddening and elevation at the focus of infection, which rapidly develops into a papule, followed in from 12 to 15 hours by a vesicle, about the size of a pea or perhaps a little larger, with a central depression containing a brownish fluid, and frequently surrounded by a slight edematous areola. Either the vesicle dries up, or its roof is rubbed off, leaving a blackish eschar which often becomes surrounded by a ring of closely-set, minute vesicles. This depressed, central necrotic eschar, resting in the cutis, spreads downward and outward and with the infiltrated area forms a sore from 2 to 3 cm. in diameter, surrounded by red and edematous tissue. Sometimes within this edematous area around the eschar a circle of new vesicles develops and as the eschar spreads peripherally the infiltration also extends, so that the lesion rapidly reaches a diameter of from 6 to 9 cm. The skin for some distance is transformed into a doughy, pinkish, edematous mass. The surrounding lymph-glands are generally swollen, painful, and covered with edematous skin. Lymphatic involvement may also extend to remote glands, as, for example, to those in the axilla when the lesion develops on the arm. A characteristic feature of the pustule itself is the absence of pain in and about the lesion. Even when it is extensive the patient complains of only a sense of weight and slight tenderness on pressure, but never of pain. Pus formation does not set in until the fourth or fifth day, when the sore begins to suppurate.

Vomiting and diarrhea are occasionally added to the clinical picture. The spleen is often enlarged, and the *Bacillus anthracis* is frequently recovered from the blood. In the meantime the local lesion has assumed a bluish hue, the surrounding vesicles become filled with a hemorrhagic fluid, while the edematous area is infiltrated with blood and sometimes undergoes gangrenous degeneration. At this time blood may also be found in the vomitus and in the thin stools. Blood-pressure is lowered; the temperature falls to subnormal, the pulse becomes smaller and the rate increases; the extremities grow cold and cyanotic, and a sticky sweat exudes from the pores. In fact, all the symptoms of collapse set in, accompanied by loss of consciousness and sometimes by convulsions just before death. The fatal course may be run in two or three days, but it may be prolonged from five to eight days. In some instances the infection spreads to the lungs, the intestines or the brain, death resulting with signs of pneumonia or with those of abdominal or cerebral phenomena. A few cases heal spontaneously, even though the specific organism has been recovered from the blood. Sometimes a mixed infection from the purulent discharge leads to septicemia with a clinical picture varying according to the superadded organism, and with a prolonged course of illness the prognosis of which is most uncertain.

MALIGNANT ANTHRAX EDEMA (Œdème charbonneux).—This disease, first described by Bourgeois in 1861, may attack the neck or the chest, or the mucous surfaces of the mouth and tongue, but most often it affects the mucosa of the eyelids. It appears in the form of a tough, pale swelling which, as a rule, is painless and semi-transparent, and though soft at first hardens as it increases in size. The typical eschar is usually wanting. The swelling soon reddens and occasionally becomes the site of small serous or hemorrhagic vesicles in which an eschar resembling that of malignant pustule develops. The course of the disease is generally more rapid and more fatal than that of malignant pustule. When it occurs on the eyelids the infection may in some instances be benign, but its presence on the buccal mucosa is always serious on account of the added danger of death from suffocation due to the extension of the edema to the tongue, the pharynx, or larynx.

INTERNAL ANTHRAX.—This appears in an intestinal form (mucosis intestinalis) and in a pulmonary form (wool-sorter's disease).

Intestinal Anthrax.—This is most frequent in animals, but comparatively rare in man. Its onset may be preceded by prodromal symptoms of malaise, weakness, headache, chilliness and sweats, but generally it is sudden, accompanied by anorexia, gastro-intestinal symptoms, thirst, nausea, persistent vomiting, diarrhea, and epigastric pain so marked as to suggest intestinal obstruction or strangulation. The abdomen becomes distended and exquisitely tender, the spleen being markedly enlarged. The patient complains of a feeling of oppression, the pulse is small and rapid, while the temperature at first may show little change. Often, however, it rises suddenly or falls and becomes subnormal just before death. The general toxemia leads to loss of strength and to collapse, resulting in death on the second or third day, often after a convulsive attack; or death may result from peritonitis. In some instances the effects of the general circulatory infection are seen in petechial or other diffuse hemorrhages in the skin, accompanied by tiny vesicles which contain a serous or hemorrhagic fluid and a typical anthrax infiltration.

In some cases where the bacillus has been ingested, a few among a group of individuals may recover, but the result is generally death within five days.

Pulmonary Anthrax.—Pulmonary anthrax results from the inhalation of dust containing the spores of the anthrax bacillus. Eurich, however, has demonstrated that the germ resides not in the dust but in the blood-stained wool and hair, the dust being dangerous because of its admixture with scales of blood from tainted hairs.

The symptoms are sometimes vague until just before death, which is preceded by sudden collapse without any premonition other than a slight indisposition. Generally the symptoms *appear suddenly* with chill, weakness, fatigue, uneasiness about the chest and upper abdomen, frequently accompanied by vomiting, with bile-stained and hemorrhagic vomitus and occasionally diarrhea, which may also be hemorrhagic. The pulse is small and rapid, the temperature rises suddenly to about 105° F. (40.5° C.) and the patient is dyspneic; the nasal mucous membrane is swollen, while small sores often appear in the nostril; the pharynx and tonsils are sometimes swollen and are covered with an easily detached false membrane. The epiglottis also is red, edematous, and enlarged. The lungs, of course, are always involved; bronchitis and bronchopneumonia are marked and accompanied by a troublesome, often unproductive, cough, the specific bacillus being found in the sparse expectorations. Frequently the difficulty in breathing is enhanced by an accompanying pleurisy, and in some instances by hemorrhagic infiltration of the mediastinal glands. The bacillus is nearly always recovered from the blood in these cases. The urine is dark and scant, sometimes showing albuminuria and increased specific gravity. In the large majority of cases death is the result, ensuing in two or three days, although a few instances of recovery have been recorded.

ABERRANT TYPES OF ANTHRAX.—In these types the symptoms are entirely cerebrospinal, such as those of acute meningitis with vomiting, headache, irregular pulse and respiration, delirium, or coma, and sometimes retraction of the head and neck. Or in another type the symptoms may be vague and not referable to any particular organ, being merely those of a profound toxemia with fever, delirium, or coma. Splenic enlargement is a constant feature of this type, which, like the former aberrant one, always ends fatally.

Diagnosis.—The diagnosis of *malignant pustule* presents few difficulties. The history, if taken with patience and careful attention to all details, will almost invariably lead back to the source of infection. Even though the patient's occupation has not exposed him to infection, it will generally be found that in some way or other he has been in contact with an infected animal or animal product.

In addition to the facts elicited by a consideration of the history, the disease is easily recognized because of the fairly constant character of the external anthrax lesion, and furthermore because of the presence of the specific organism in the vesicles, smears of which will furnish prompt and reliable evidence of the nature of the affection. If desirable, diagnosis can be confirmed by animal inoculation, although this is rarely necessary.

Internal anthrax, on the other hand, is not so easily recognized; in fact, diagnosis is very often not made until postmortem.

Intestinal anthrax should be suspected in the presence of hemorrhagic stools, especially when associated with a history of eating insufficiently cooked meat of animals subject to anthrax, or in the case of workers in whom the disease might be due to their occupation, where one may suspect a history of eating without proper precautions as to cleanliness of the hands, and where the germ would be likely to be ingested with food that had become infected from the fingers. Diagnosis in these cases is sometimes made by the recovery of the bacillus from the feces or from the blood.

Pulmonary anthrax should be suspected in all cases which present symptoms of pneumonia or bronchopneumonia occurring among individuals whose occupation favors anthrax infection. Blood in the sputum, and the presence in the latter of the typical bacillus, should clinch the diagnosis. Blood cultures will also prove useful in establishing the true nature of the disease, since in most instances of this type the organism circulates in the blood. Finally, the simultaneous appearance of a skin lesion in conjunction with symptoms suggestive of either variety of anthrax should render the diagnosis certain.

The *aberrant types of anthrax* are practically never diagnosed.

DIFFERENTIAL DIAGNOSIS.—Should any doubt exist, the differentiation of *malignant pustule* from other sores or skin lesions can be made on the basis of the painless character of the malignant sore and the presence of a surrounding halo of vesicles.

Glanderous nodules on the face often suggest anthrax, but they are usually multiple, painful, and accompanied by some disease of the mucous membranes. The differentiation from *pyogenic abscess* can generally be made on the basis of the absence, in the latter, of constitutional symptoms. Malignant edema, especially of the eyelids, may sometimes be confused with *erysipelas,* but the early appearance of tense infiltration and the presence of vesicles in anthrax should assist in distinguishing the disease from erysipelas.

Treatment.—PROPHYLAXIS.—Since human anthrax is contracted only from infected animals, the primary factor in its prevention or eradication in man is its prevention among animals. Nearly all the states of the United States have enacted laws which, although not specifically directed toward the prevention of anthrax, forbid the importation of animals affected with infectious or contagious diseases and require the quarantine of diseased cattle or of those that have been exposed to disease. But in view of the increased incidence of anthrax in this country within comparatively recent years, direct federal legislation has been introduced for the prevention of the disease. This legislation comprises more stringent laws with regard to the importation into this country of animal products from countries, such as Russia, China, and some parts of Asia, in which anthrax prevails and in which sanitation is not highly developed. Furthermore, the law requires that all material coming from infected centers must be properly disinfected or otherwise treated to reduce or remove the danger of anthrax infection.

But this does not suffice to protect the industrial workers. Their protection should be further increased by simple precautions in the handling of suspected material. All workers should be required to wear gloves when handling such material (wools, hides, etc.). A wise precaution is the habit of wearing overalls or changing the street clothes and putting on work-clothes. The best arrangement is that which provides three rooms for the worker: one in which the street clothes are laid off, a second room through which he passes into the third room, where he puts on his work-clothes. When coming from work he leaves his clothes in this last room, passes into the second room, which is a lavatory, and after a thorough cleansing of his hands, face, and other exposed parts, he passes into the outer room, where he puts on his street clothes. Personal cleanliness is a matter of the greatest importance. Employers should be required to provide sanitary wash-rooms with plenty of hot water, soap and individual or paper towels for the use of the employees. Especial attention should be paid by the latter to keeping the finger-nails clean, as the bacillus is very apt to lodge there.

The walls and floors of the workrooms and work-benches should be frequently cleaned with soap and water, and special devices should be arranged for the elimination or absorption of dust, especially in wool-sorting establishments where the danger of contracting the serious and fatal pulmonary anthrax is greatest. Employees in such industries or in similar ones should by all means be compelled to wear masks. With the experience gained during the war in protecting the respiratory organs against dangerous gases, there should be no difficulty in devising a suitable mask to protect these workers. As an additional safeguard notices should be prominently placed in all factories dealing with material liable to harbor the anthrax bacillus or its spores, indicating to the workers the manner in which infection occurs, warning them of the danger of eating in the workroom, and also of the risk of exposing slight abrasions on the skin to infection, and the importance of prompt and early treatment at the first sign of infection, such as a small pimple or sore. A first-aid kit containing iodin and dressings should be part of every establishment of this kind. Finally, anti-anthrax serum should be provided at a small cost, if not free, to all workers in these industries.

General Treatment.—Opinion is by no means uniform as to the best method of treating human anthrax. Some physicians, on the theory of the natural power of resistance of the body to infection, advocate a semi-expectant treatment, consisting of **rest, fixation** (rest) **of the lesion,** and either **serum therapy** or the local application of **ointments** such as **mercuric chlorid,** or of **hot compresses** or cataplasms, followed by **injections** of **carbolic acid** or **mercuric chlorid;** others have reported success with the local application of **salvarsan** or **neosalvarsan.**

SURGICAL MEASURES.—While in some instances in the author's experience successful results have attended fixation (rest) of the lesion and serum therapy, it is his belief that malignant pustule is best treated by **excision,** followed by serum therapy and local and systemic treatment. Knowing the very serious nature of anthrax, there should be no hesitation in using all the therapeutic agents at our disposal, i.e., surgery, internal and local medication. The writer therefore practices excision followed by the application of powdered **ipecacuanha** to the wound, and serum therapy together with supportive postoperative treatment.

Excision.—**Excision** should be the first measure resorted to, for the earlier it is done, the more favorable will be the prognosis and the better the cosmetic results. With the patient under ether anesthesia, the incision should be made large enough to include the lesion and the surrounding reddened area, but need not go beyond this. The resulting wound and surrounding area should at once be thoroughly swabbed with **tincture of iodin;** on the following day the area around the wound is again painted with iodin and the wound crater itself filled up with powdered **ipecacuanha.** Immediately after operation **anti-anthrax serum** is injected intravenously in doses of from 40 to 100 c.c., according to the severity of the case. The dose can be repeated every six to twelve hours as often as necessary in a given case; mild cases will require only the initial dose of 40 c.c.

Supportive Measures.—In the favorable cases, local improvement sets in immediately after operation, the edema subsiding with remarkable rapidity, the general condition showing no less marked improvement. Treatment after this is symptomatic, consisting mainly of **supportive measures** during the acute stage. A liquid **diet** is advisable for at least two days after operation. **Buttermilk** has been found useful in some instances. After the acute stage is passed, provided the urine is negative and the general condition warrants it, the patient may rapidly be put on a full diet. The average case can be dismissed in about ten days, even though the wound has not entirely healed. Such patients should be instructed as to the proper precautions against infecting the wound, which should be dressed by a competent physician.

This method of treatment has given splendid results in the author's experience, which during eleven years of service covers 61 cases with 14 deaths, a mortality of 23 per cent. (Four of the fatal cases were moribund when admitted.)

SERUM THERAPY.—Recovery from a spontaneous infection is supposed to provide immunity against a second attack. On the basis of this theory it has also been proved that this immunity can be induced artificially in highly susceptible animals by means of **attenuated cultures** or by the **products of the anthrax bacillus.** Pasteur demonstrated that frequent treatment with attenuated cultures immunized animals against experimental as well as against spontaneous anthrax infection. He obtained this active immunization by inoculating sheep, cattle, and other animals with attenuated cultures grown at 42° C. (which he called Vaccine I). In this vaccine given at the first dose the potency of the organism was affected so as to be virulent for mice but not for guinea pigs or rabbits. But the second dose (Vaccine II) was found to be virulent also for guinea pigs.

The systematic application of this theory of immunization, representing as it does the foundation of active immunization against infectious disease, has been an important factor in the prevention of anthrax. But often, owing to the difficulty of exactly estimating the virulence of the toxin, the result, instead of immunization, was a virulent infection followed by death. This has, however, now been overcome by the happy thought of *combining active with passive immunization.* Sclavo, Sobernheim, Marchoux and others have shown that the serum of animals thus immunized contains protective antibodies, and they have obtained a high potency serum that acts as a prophylactic for animals and at the same time as a therapeutic agent for human anthrax.

The pioneer work of serum therapy, however, was done by Toussaint (in 1880), who injected the heated blood of animals dead of anthrax into other animals, the latter being subsequently found immune to infection with virulent anthrax bacilli. Later on the successful production of antitoxins in the treatment of diphtheria and tetanus stimulated investigators in the search for a similar means of curing anthrax. Marchoux, in 1895, produced an efficacious anti-anthrax serum in the treatment of experimental anthrax in animals, but the preparation most widely employed in Europe, especially in Italy and England, is that obtained by Sclavo in 1902 and 1903. With this, animals are immunized by the injection of attenuated cultures of the anthrax bacillus followed by injections of more virulent cultures. The immune serum thus obtained is then introduced into the human subject either by the intravenous or the intramuscular route. At first Sclavo used small doses of from 10-50 c.c., but after continued experience it has been found that only large doses of from 60 to 80 c.c. are effective, and that the earlier the administration the more favorable the results. Recovery ensues in nearly all cases, even in the moderately severe ones, if the serum is used early. Furthermore, the destruction of tissue is reduced to a minimum, while for lesions that cannot be reached by the knife it is the only available method.

At the Philadelphia Hospital for Contagious Diseases, **Sclavo's serum** is the one generally employed, but of late when, owing to the war, this was not always obtainable, other preparations have been found equally efficacious.

The precise action of the serum is not known. It is supposed by some to be largely bacteriotropic and bacteriolytic, and by others phagocytic, but no definite conclusions have as yet been arrived at as to the presence of specific immune substances in anti-anthrax serum, although the clinical evidence of its curative powers is unmistakable. This is well demonstrated in the case reported by Regan and Regan in which, for a lesion on the neck, in addition to intramuscular injections, they injected the serum locally into the indurated tissues immediately around the lesion and obtained a cure without resorting to the knife. Except for a temporary, febrile, serum reaction, improvement was uninterrupted. The lesion, in drying, left a thick adherent crust which was removed with difficulty, leaving raw, ulcerative surfaces. These were treated with tincture of iodin and, when finally healed, there remained only a small, slight, depressed, circular scar, about the size of a dime. The author believes the method a rational one and well worth trying.

In South American countries, where anthrax is widely prevalent, **normal beef serum** has recently been introduced by Kraus, Beltrami, Penna, and others, the results being acclaimed with great enthusiasm by these authors. The serum is heated twice to 56° C. (132.8° F.) for half an hour, to eliminate the toxic effect of beef serum, and is used in doses of from 10 to 20 or 30 c.c. at each injection in ordinary cases, and increased to 40 or 50 c.c. in severe ones. In a series of 146 cases thus treated the mortality was 0.68 per cent. These investigators find that serum sickness follows in comparatively few instances (only two are reported in the series) and that the local and general effects are remarkably prompt. The method has been opposed by Lignières on account of the greater toxicity of normal beef serum as compared with immunized horse serum; he also offers the rather specious argument that as cattle are subject to anthrax, it would seem that if their serum contained any natural defensive properties, these should protect the cattle from the disease. In this country the successful use of the method has been reported by Hyman and Leary. In commenting on it these authors conclude that anti-anthrax serum owes its activity in a small degree to specific immune substances and a large degree to a nonspecific proteid reaction. For the latter purpose they believe that heated beef serum is the blandest foreign agent that can be introduced into the human system. They have also noted the absence of serum sickness, and advocate the use of normal beef serum for this reason as well as because it is so much less expensive than immunized horse serum.

Prognosis.—The prognosis of *external anthrax* is largely dependent upon the promptness and vigor with which appropriate treatment is instituted, and to some degree upon the extent of the process and its duration. Andrews estimates the gross mortality from the disease at about twenty per cent., but for cases in the hands of individual practitioners who institute prompt treatment very much lower figures are reported. The site of the lesion is of importance from a prognostic viewpoint, for it is well known that a lesion on the neck, for example, may cause the edema to spread to the larynx and the mediastinum and lead to death from asphyxiation. Extensive edema is a bad omen, as is also the presence of constitutional symptoms, especially when they indicate involvement of the central nervous system, although patients with external anthrax accompanied by marked constitutional symptoms have been known to recover. As to *internal anthrax,* the fact that it is so rarely diagnosed is sufficient indication of its gravity. In the cases that are diagnosed a fatal outcome is inevitable if the bacillus is found in the blood; although a few cases may recover, they are very exceptional.

Pathology.—The virulence of the anthrax bacillus is seen in the rapid changes that take place postmortem. The body becomes black in two or three hours and decomposition sets in early. The tissues about the neck and chest become the site of a putrid emphysema, sometimes with great distention. A brownish fluid runs from the mouth and other orifices, while the serous fluid is almost black in color.

In nearly all cases of *external anthrax,* in addition to the edema at the site of inoculation, secondary lesions are found in various parts of the body, consisting mainly of a characteristic, gelatinous, serous or sometimes hemorrhagic effusion into the surrounding tissues.

The *heart-muscle* and the *pericardium* are the site of more or less extensive hemorrhage.

Characteristic of anthrax is the enlargement of the *bronchial glands,* which are surrounded by ecchymoses and hemorrhage. The bases of the *lungs* are hemorrhagic and are also the site of the gelatinous or serous effusion, while large pleural and pericardial effusions are not uncommon.

In the *stomach* and *intestines* the lesions are seen in the form of patches of gelatinous or bloody infiltration in the submucous tissue; similar foci are found in the omentum and the mesentery, while the peritoneal cavity is also often filled with fluid.

The *liver* and *kidneys* show cloudy swelling and enlargement, together with evidence of hemorrhage under the renal capsule.

The *spleen* is often, though not always, enlarged, congested, and soft; when enlargement is marked it is diffluent and black in color.

In the *central nervous system* also one notes hemorrhagic infiltration into the meninges or sometimes into the cortex of the brain and the pia mater, or into the substance of the spinal cord. Edema spreading from the neck to the larynx or to the mediastinum is commonly seen.

The *blood* shows marked leukocytosis with a predominance of polymorphonuclear cells.

The lesion that results from invasion of the anthrax bacillus into the *skin* represents a tough cellular infiltration with a central eschar composed of epithelial degeneration and of necrotic skin tissue. The cellular infiltration involves the surrounding connective tissue, which is also engorged with serous infiltration, sometimes accompanied by extravasation of blood and fibrinous exudate. According to some authorities, the bacilli are found in small numbers in the superficial layers of the pustule, but they are nearly all dead; sometimes pyogenic organisms, especially streptococci, are also present. In the deeper layers the bacillus is found in large numbers, but here also not in an active state.

The most viable organisms are those found in the edematous area around the lesion itself. In anthrax edema, in which the local lesion does not develop, the changes consist of serous cellular infiltration of the skin and the cutaneous connective tissue with foci of hemorrhage and sometimes circumscribed areas of gangrene.

In *internal anthrax* a blood-stained fluid is found in the swollen mucous membrane of the lower part of the trachea and the bronchi. The enlargement of the *bronchial glands* is likewise noted and there is also evidence of hemorrhage and of serous effusion into the *mediastinal tissues.*

The *lungs* are hemorrhagic, while serous exudation is found in the pleural, pericardial and often in the peritoneal cavities.

The local lesions in *intestinal* anthrax are found chiefly in the stomach and the small intestine. They consist of slightly elevated, dark-red hemorrhagic areas surrounded by an injected edematous zone, sometimes with an ulcerated or gangrenous center, on the surface and also in the deeper structures of which the anthrax bacillus is found in large numbers. Under the microscope the capillaries are seen to be dilated, and there is also evidence of hemorrhage. The bacillus appears to exhibit the same selective action for the lymphatics of the intestine as is characteristic of the typhoid bacillus. Peritonitis is often marked and *splenic* enlargement is also quite common.

In 2 cases of intestinal anthrax reported by Zingher he noted extensive *cerebral hemorrhage* covering both hemispheres within the pia and the arachnoid and extending into the sulci, dipping in between the convolutions. Cultures of the *blood* and the *cerebrospinal* fluid just before death showed the presence of *Bacillus anthracis*, which was also found postmortem in the intestinal lesions.

In *pulmonary anthrax* the characteristic lesion is present in the lower trachea and the larger bronchi. The bacillus is found in large numbers in the mucous and submucous tissues, especially in the lymphatics and the lymphatic plexuses around the arteries. The substance of the membrane is infiltrated, and exudation followed by hemorrhage takes place beneath the epithelium.

Historical Summary.—Anthrax dates back to very ancient times; in fact, it is supposed to be identical with the murrain mentioned in Exodus. Classical writers, Virgil and others, allude to it as though it were the only disease among animals worth mentioning. In ancient and medieval history it figures largely as a devastating pestilence which attacks animals and through them man. Old Anglo-Saxon manuscripts contain curious accounts of recipes, charms and incantations for the prevention and cure of "black bain," the term by which anthrax was known. Although destructive epizoötics of the disease spread over Europe during the Middle Ages, it was not until toward the end of the 16th century that it began to be suspected that animal anthrax was transmissible to man by contagion from infected animals.

Chabert, in a book on anthrax in man, in 1780, was the first to distinguish the different forms of the infection from other septic and gangrenous skin diseases which were at that time included under the term anthrax. Although he described three forms of the disease—internal anthrax, malignant pustule, and symptomatic anthrax—he failed to recognize that the latter (now known as black quarter, or Rauschbrand) is a distinct disease in animals and not communicable to man. Little was added to our knowledge of anthrax after this time until 1823, when Barthélemy, by experiment, proved its contagious character in animals. Heusinger, in 1850, in his classical work on the epidemiology of human and animal anthrax throughout the world, expressed the belief that it was due to a malarial neurosis dependent upon certain conditions of the soil and the climate.

The discovery of the specific cause of the malady was destined to await the advent of bacteriology into the domain of medicine. The bacillus of anthrax, according to Ravenel, was first described in 1850 by Rayer and Davaine, although Pollender subsequently announced that in 1849 he had observed the same organisms as described by them, and had recognized their vegetable nature, but had failed to attribute any importance to them. Nor did Rayer and Davaine at first realize the significance of their discovery of small, non-motile, filiform bodies "about twice the size of a red blood-corpuscle" which they observed in the blood of animals affected with anthrax. In 1857 Brauell observed the same type of organism in man just before death, and by inoculations into animals he succeeded in producing the disease. Although he recognized the importance of the presence of the organisms from a prognostic point of view, he failed to establish their causal relation to the malady. In 1860 Delafond made cultures of anthrax blood and observed that when developing *in vitro* the organisms assumed the form of long, undulating filaments instead of the short rods. He furthermore stated his belief that they originated from spores without, however, arriving at any conclusions as to whether they were the result or the cause of the disease. Finally, in 1859, Pasteur's epoch-making studies on the influence of microbes in the process of putrefaction, fermentation and the various forms of disease laid the foundations of modern bacteriological research and opened up the way to other investigators. Thus stimulated, Davaine, in 1863, again took up the search for the cause of anthrax, which he began to suspect could be traced to the organism he had previously described. After untiring study he was finally able, in 1873, to demonstrate the constant presence in the blood of anthrax animals of the organism which he designated as *bactéricide du charbon*, and to prove furthermore that the blood, when filtered, could be inoculated into other animals without harm. These facts were later confirmed by Robert Koch, in 1876, who by his method of developing pure cultures of bacilli on solid media also discovered the spores of the *Bacillus anthracis* and proved their etiological relation to the disease. The truth of the findings was further demonstrated by Pasteur, who, in 1877, announced the small non-motile rods first described by Rayer and Davaine to be the specific cause of anthrax.

BIBLIOGRAPHY

Amory, O. T., and Rappaport, B. Anthrax at the evacuation hospital at Newport News. Jour. Am. Med. Assn., 1919, lxxii, 269.

Andrews, J. B. Anthrax as an occupational disease. U. S. Bureau of Labor Statistics, Bull. No. 205. Washington, 1917.

Angevine, R. W. Anthrax septicemia from accidental inoculation of shaving wound. Boston Med. and Surg. Jour., 1919, clxxx, 149.

Bourgeois. La pustule maligne et de l'œdème malin. Paris, 1861.

Brauell. Versuche und Untersuchungen betreffend Milzbrand des Menschen und der Thiere. Virchow's Archiv, 1857, xi, 132.

Brumbaugh, A. S. Anthrax enteritis. The morbid anatomy and histology of two cases at Camp Dodge, Iowa. Jour. Am. Med. Assn., 1919, lxxii, 483.

Chabert, P. Déscription et traitement du charbon dans les animaux. Paris. 1780.

Davaine, C. Récherches sur la nature de la maladie charbonneuse. Compt. rend. Acad. de sc., Paris, 1864, v, 1296.

——— Essai de traitement du virus charbonneux. Rev. Phot. d. hôp. de Paris, 1873, v, 221.

Elworth, R. R. An outbreak of anthrax conveyed by infection from shaving brushes. Lancet, 1916, i, 20.

Eurich, F. W. The administrative control of anthrax. Jour. Roy. San. Inst., London, 1908-09, xxix, 597.

Heusinger, C. F. Der Milzbrand. In: Krankheiten der Thiere und des Menschen. Erlangen, 1850.

Hyman, C. H., and Leary, T. The treatment of anthrax with normal beef serum. Review of the literature with report of case. Boston Med. and Surg. Jour., 1917, clxxviii, 318.

Koch, R. Zur Aetiologie des Milzbrandes. Mitt. a. d. k. Gesundheitsamt, 1881, i, 49.

Koch, W. Milzbrand und Rauschbrand. Deutsch. Chir., 1886, pt. 9.

Kraus, R., and Beltrami, P. El suero anticarbuncloso; parte experimental. Prensa méd. argentina, 1916-17, lii, 225-227.

Leake, J. P., and Lederer, A. Isolation of anthrax bacillus from shaving brushes. Am. Jour. Pub. Health, New York, 1919, ix, 114.

Legge, T. M. Industrial anthrax. Lancet, 1905, ii, 689; 765; 841.

Lignières, J. Sobre el tratamiento del carbunclo con el suero normal de bovino. Rev. Asoc. méd. argent., Buenos Aires, 1916, xxv, 587.

Ludy, J. B., and Rice, F. C. Anthrax at Camp Hancock, Ga. Jour. Am. Med. Assn., 1918, lxi, 1133.

Marchoux, E. Sérum anticharbonneux. Ann. de l'Inst. Pasteur. Paris, 1895, ix, 785.

Pasteur, L. Étiologie des maladies charbonneuses. Bull. Acad. de méd., Paris, 1877, vi, 921; vii, 752; viii, 1063.

——— Le vaccin du charbon. Jour. de pharm. et chim., Paris, 1881, iii, 542.

——— Sur la vaccination charbonneuse. Compt. rend. Acad. d. sc., Paris, 1883, xcvi, 979.

Pasteur, L., Chamberland, C., et Roux. Sur l'étiologie du charbon. *Ibid.*, 1880, xci, 86.

Penna, Bonorino Cuenca, J., and Kraus, R. Sobre el tratamiento del carbunclo con el suero normal (3ª comunicación). Prensa méd. argent., Buenos Aires, 1917-18, iv, 91.

Pollender. Mikroskopische und Mikrochemische Untersuchung des Milzbrandblutes. Vierteljahresschr., f. gerichtl. Med., 1855, viii, 103.

Ravenal, M. P. Anthrax, rabies and glanders. In: Osler's Modern medicine, Vol. III, Philadelphia, 1907.

Regan, J. C., and Regan, C. Human anthrax. Am. Jour. Med. Sc., June, 1919, clvii. 782.

SCHULTZ, O. T. Two cases of human anthrax at Camp Jackson. Jour. Am. Med. Assn., 1918, lxxi, 1571.

SCLAVO, A. Sullo stato presente della sieroterapia anticarbonchiosa. Riv. d'ig. e san. pubb., 1903, xiv, 519.

SOBERNHEIM, G. Ueber das Milzbrandserum und seine praktische Anwendung. Deutsch. med. Wchnschr., 1904, xxx, 571, 948, 988.

SOLARI, E. F. Tratamiento del carbunclo humano con el suero normal de bovino. Semana méd., Buenos Aires, 1917-18, iv, pt. 2, 98.

TOUSSAINT, H. Procède pour la vaccination du mouton et du jeune chien contre la maladie charbonneuse. Bull. Acad. de méd., Paris, 1880, ix, 792.

ZINGHER, A. Two cases of intestinal anthrax with small skin lesions and extensive meningeal hemorrhages. Proc. New York Path. Soc., 1918, xviii, 69.

CHAPTER XLII

TETANUS

By S. Potter Bartley, M.D.

Definition, p. 25—Etiology, p. 25:—Predisposing causes, p. 25; Exciting causes, p. 26—Symptomatology, p. 28:—Clinical history, p. 28; Physical findings, p. 30; Laboratory findings, p. 30; Special examinations, p. 31—Diagnosis, p. 31—Complications, p. 32—Clinical varieties, p. 32—Treatment, p. 36:—Prophylaxis, p. 36; General management, p. 38; Symptomatic treatment, p. 38; Surgical treatment, p. 40; Antitoxic treatment, p. 40:—Phenol treatment, p. 40; Specific serum (antitoxic), p. 40—Prognosis, p. 43—Pathology, p. 44—Statistical summary, p. 45—Distribution, p. 46; Bibliography, p. 46.

Definition.—Tetanus is a disease caused by an infection with the *Bacillus tetani*, and characterized clinically by a toxemia in which the central nervous system is attacked, producing tonic spasm of the muscles.

The infection has long been known as one of the most dreaded of diseases. The mental anguish and physical suffering are probably greater than in any other known disease, except possibly in hydrophobia.

Etiology.—Predisposing Causes.—The most important predisposing cause of tetanus is the *wound*. This is generally traumatic, but may be of any type, from the large wound of the shell fragment, to the minute wound of the hypodermic needle.

The *Bacillus tetani* is undoubtedly of telluric origin. The spores are frequently found in the manure of the horse and are present in the intestinal tracts of a large percentage of the herbivora.

The bacillus occurs most frequently on the surface of the *soil*, but it is also present to a large degree in dunghills, manure pits, etc. The infection is contracted through a wound which has been contaminated by dust, particles of earth, clothing, etc., due to improper protection or to special circumstances (as during the Great War, when the wounded were lying out on the ground or had to crawl to cover over infected soil). These circumstances and the soil contamination of certain areas in France and Belgium account for the incidence of tetanus during the war. The disease was less frequent after the battles around Ypres, than in the valley of the Aisne (Bowby). The rich clay of Flanders is quite different from the dusty, calcareous soil of Champagne. That certain soils are rich or poor in tetanus spores has been established by scientific investigation. Veterinary surgeons have long testified to this fact, and investigators during the war have proven it to be true.

The presence of other microörganisms favors the growth of tetanus spores, as the phagocytes are drawn to the other bacteria which are present, and thus allow the spores of tetanus to develop.

Severe heat or cold are factors favoring the development of tetanus. Humidity probably has no effect, as the spores in dust produce the infection, when they incubate in the wound moisture.

Secondary infection or mixed infection seem to play an important rôle in the development of tetanus. The resistance of the patient is low, especially if the wounds are multiple or if wound-sepsis is present. Villard and Vincent have shown that the injection of spores free from toxin, plus cultures of *Bacillus prodigiosus*, causes a very virulent and mortal tetanus. Using a staphylococcus or streptococcus as an associated organism these experimenters were unable to produce tetanus.

Extensive wounds of the soft parts where there is great destruction of muscle and open articulations with suppuration predispose to tetanus. Especially wounds of the extremities or of the head, containing dirt, clothing and foreign bodies, should be regarded as highly suspicious. That tetanus can be transmitted from one person to another is more than a hypothesis. Tetanus cases should be isolated. In support of this fact Duteitre reported the history of three men placed in adjacent beds who developed tetanus. Of five patients who were placed in the same room, three were infected, and transmitted tetanus to the other two by touching their dressings with their hands. Nurses and surgeons should use due precautions in handling the dressings and wounds of tetanus cases and should manage them as they do any other infectious disease. The male seems to be more often infected than the female, due to the greater degree of exposure to infections through war wounds or to the trauma incident to civil life. Young adults and children also show a higher percentage of infection.

Exciting Causes.—The direct cause of tetanus is the inoculation of the human organism with the *Bacillus tetanus*, generally as a wound infection. The modes of entry are many: Tetanus is liable to occur in any wound which has been contaminated with manure, garden soil or, in the cities, with street dirt. The soils of certain regions are more highly infected than others. Gunshot wounds, especially those produced by blank cartridges, should be considered as potentially infected with tetanus, for, in the United States, many fatal cases of tetanus have followed fourth of July wounds. Antitoxin, virus, and vaccines have been contaminated by tetanus spores and have caused tetanus when injected. This accident is now controlled by law, which was established following an unfortunate experience in St. Louis in 1901 (Waldon and Fisch). Solutions of gelatine have been known to be contaminated with tetanus spores, and they should be thoroughly sterilized before injections. Cat-gut has also been known to be contaminated and has given rise to postoperative tetanus infections. Tetanus may follow cord infections in the new-born or may occur in the mother following accouchement. Postoperative tetanus has occurred where the portal of entry was the operative wound. The highest percentage of infection has followed operations on the intestinal canal, such as the closure of a fecal fistula. In these instances, the infection was thought to be due to the presence of the *Bacillus tetani* in the contents of the intestinal canal. However, the most common mode of infection is the traumatic wound, especially when containing foreign bodies.

Bacteriology.—The bacillus of tetanus was discovered by Nicolaier in 1883. He demonstrated the bacillus in the pus from animals which had developed clinical tetanus after the injection of small quantities of earth. The specific character of the bacillus was proven by Kitasato, who isolated and cultivated it. He then produced clinical tetanus by inoculation with cultures. Villard, Vincent, and Rouget are credited with working out the condition under which tetanus developed. The studies of tetanic toxin by Villard and Roux gave us antitetanic serum, one of the specific sera of medicine.

The *Bacillus tetani* may be found in the pus of tetanic wounds. It is rod-shaped; the ends, however, are not round. The general measurements are 4 to 5 microns in length by 0.3 micron to 0.4 micron in breadth. The spores are generally absent. The characteristics of the organism vary with the age of the culture. Early cultures (from three to four hours) in bouillon give the same characteristic organism which we find in wound pus. The bacillus sporulates after from eight to ten hours' cultivation. It then appears as a slender rod with a round refractive spore at either extremity, giving the bacillus the appearance of a club. As the bacillus grows the rod disappears, leaving only the spore. This process begins only after about the tenth day. In the absence of oxygen, mobility may be demonstrated in fresh material. This mobility is very slight and disappears with the formation of the spores. The *Bacillus tetani* is Gram-positive and will take the basic aniline dyes. Those with spores take the stains only in the rod or bacillary part and around the rim of the spore, the center remaining refractive and without stain. Vibratory cilia may be present before the spore is formed.

For culture of the organism, the usual media are satisfactory, provided they are anaërobic and prepared with fresh bouillon. Albuminous media do not grow good cultures. On the other hand, rabbit serum grows a very virulent organism. The colonies on gelatin make their appearance on the fifth day. They are small, round, and cloudy, with needle-like filaments growing from their periphery, and are surrounded by small gas-bubbles.

In bouillon cultures, after fifteen days, the bacilli sink to the bottom of the tube. When the cultures are opened they give off an odor of burnt horn. Potatoes are poor media. Milk grows the bacillus well, without coagulation, if protected from light and air.

The vitality of the spore lasts for several years. The spores will resist boiling for four or five minutes and withstand a temperature of 80° C. (176° F.) for from five to six hours. Nocarde found organisms, taken from colts dying from tetanus, alive after eighteen months. A splinter taken from the hand of a patient with tetanus and kept for two and one half years in a closet caused tetanus when inoculated into an animal (Eiselberg).

Agglutination will occur with the serum of a horse vaccinated against tetanus, at 1-2000 dilution, but not with human or other animal antitetanic serum. Most animals are easily infected with tetanus. The guinea-pig, mouse, and rat are best for inoculations. The dog has a very high resistance, while pigeons and domestic fowls show an almost complete resistance.

Tetanic pus or laboratory cultures, when inoculated into these animals, will cause tetanus. At the point of inoculation a tumor appears, varying in size. After an incubation period of three or four days the animal shows tonic contractures in the region of the inoculation, which later becomes generalized, accompanied by convulsive seizures, and the animal dies within thirty-six to forty-eight hours. Necropsy of these animals shows an abscess at the point of inoculation which may yield the *Bacillus tetani* in the pus. The other organs show no changes. The blood is always sterile to culture.

The existence of tetanotoxin was established by Faber in 1890. It may be prepared by the inoculation of fresh, peptonized bouillon. This is incubated at 37° C. for from 18 to 20 days, then filtered through a Chamberland filter. The lethal dose of the filtrate for a mouse is 0.001 c.c. The exact nature of the toxin is not known. In some characteristics it resembles the diastases. Exposure for one half hour to a temperature of 65° C. modifies it, and exposure for three hours at 80° C. renders it harmless and non-toxic. Protected from light and air, in a closed container, it may retain its toxicity for months. Like the diastases, on the addition of calcium chlorid, the precipitates of phosphate of calcium and aluminum are thrown down. These, when washed in sterile water and injected under the skin of the guinea pig, will cause tetanus. The toxin has a special affinity for the cells of the nervous system. It is absorbed by the peripheral nerve-filaments and travels along the axis cylinders to the nerve-centers.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The period of incubation in tetanus is generally from four to ten days, but it may vary from two days to seventy or more. Patients who have received prophylactic injections show a longer incubation period, as do also the atypical forms of tetanus, especially local tetanus. The symptoms of the incubation period, or the prodromal symptoms, are of the utmost importance in early diagnosis and in the determination of treatment. The cure of acute tetanus can only be hoped for by early treatment.

Mode of Onset.—The onset of tetanus is often insidious and early symptoms are easily overlooked.

The patient may not complain of *subjective* manifestations, but by observation or questioning the following symptoms may be discovered:

(1) A slight feeling of tension or contraction, especially in the region of the wound.

(2) Insignificant pain in the facial muscles.

(3) Pain in the back without apparent cause.

(4) Slight difficulty or pain on swallowing, with negative throat inspection.

(5) Frequent urination with pain.

(6) Constipation.

(7) Cramp-like pains in the muscles, especially near the wound. Cramps arising when the patient is startled by a noise.

(8) Headaches.

(9) Restlessness, especially at night.

The early *objective* symptoms are:

(1) A tendency toward sweating.

(2) A slight increase in pulse-rate.

(3) Restlessness, especially during sleep.

(4) Retention of urine.

(5) Twitching of the muscles in the region of the wound, which may show irregular clonic contractions. A slight tap with the finger or an instrument may cause clonic contractions, spreading to other muscles.

(6) A tonic spasm of the muscles, especially the flexors, in wound regions.

(7) An increase of reflexes; those in the wounded limb often show "double jerk," throwing the muscles of that limb into tonic spasm.

(8) Anxious expression of the face.

These prodromal, classical symptoms of tetanus, although trivial, may last for days before the acute symptoms occur; generally they increase in severity in proportion to the toxemia. At times the localized muscle symptoms exist for weeks before becoming generalized, especially in cases which have had prophylactic treatment. In other cases, with short incubation periods, the onset may be rapid and severe, with early trismus and general symptoms which become rapidly more severe. Sooner or later, as the disease progresses, the signs become generalized and acute tetanus develops.

Objective Symptoms of Acute Tetanus.—(1) Tonic muscle-groups far from the site of the wound become involved; at first, there are spasms, generally of the masseters, posterior cervical, abdominal wall, spinal muscles, and of the flexors of the extremities. These tonic contractures are acutely painful and occur spontaneously or following sensory stimuli, either optic, acoustic or tactile. These contractures may produce the classical *opisthotonos of tetanus.* The muscles of the face may contract, the forehead becomes wrinkled, the lips drawn back, the teeth bared, giving the classical facies *risus sardonicus.*

(2) These symptoms are accompanied by a rise in temperature, generally slight. The pulse becomes rapid and poor in tension and volume. It is 100-130 in most cases with low temperature. Rare cases show hyperpyrexia.

(3) Sweating is profuse and the patient shows varying amounts of cyanosis.

(4) Trismus (lock-jaw) may occur early or late in the disease. The

jaws become firmly set and the patient cannot open his mouth. Trismus is not always complete; it may be possible to open the mouth half an inch. When trismus develops, the muscles of the neck stand out like whipcords and are rope-like to palpation.

(5) As the disease progresses in severity, involvement of the diaphragm and laryngeal muscles may occur. The diaphragm becomes fixed in inspiration, occurring with the general convulsions. The larynx contracts, the patient becomes very cyanotic, and asphyxiation may occur. These respiratory symptoms are very severe and give an unfavorable prognosis. Their onset is usually forewarned by epigastric pain, which may occur days in advance, and is a valuable prognostic sign.

(6) Hydrophobic symptoms occur in severe cases and these also give an unfavorable prognosis.

(7) Laryngeal stenosis may occur from contractures of the larynx and may, if continuous, demand tracheotomy.

Subjective Symptoms.—Subjectively the tetanus patient complains of severe thirst and exhaustion. Pain is felt with each spasm and the patient states that he feels "as if held in a vice." All external stimuli cause convulsions, pain and discomfort. The mentality is not altered, and the patient is very anxious about his condition. He suffers horrible mental and physical anguish.

PHYSICAL FINDINGS.—The physical findings are mostly those obtained by observation of the above symptoms. Palpation of the groups of muscles involved reveals a board-like rigidity which is increased by percussion. Any examination of the patient causes a spasm of the muscles involved. Of the *special tests* the reflexes are of interest, as they are almost always exaggerated. The knee-jerk is generally violent and is followed by tremors of the thigh muscles. In other cases a violent spasm of the hamstring group may occur, giving a "double jerk." Exaggerated plantar stimulation and ankle clonus may be obtained, the spasm extending as far up as the thigh. The reflexes of the arms are not commonly increased. Occasionally patients show crossed reflex in the lower limbs. Any group of muscles involved shows a marked hypertonicity to mechanical stimulation.

Examination of the wound at this time shows nothing typical of tetanus. The situation of the wound may be of value, as wounds of the extremities and head are more liable to tetanic infection. Puncture wounds are always suspicious. The degree of suppuration and surrounding inflammation of the tissues is not in any way characteristic. The cases with a prolonged incubation period may, upon examination, show the wound to be completely healed.

Wounds of a trivial and superficial nature are as common as more severe ones. All wounds should be carefully examined for the presence of foreign bodies such as dirt, clothing, fragments of metal (projectiles), splinters, etc., as these are very often the cause of tetanic infection.

LABORATORY FINDINGS.—The laboratory findings are very meagre in tetanus.

The urine is generally diminished in amount, is of high specific gravity, and may contain albumin and hyaline casts, if the kidney has been damaged by the elimination of the toxins.

In "serum sickness" the albumin content may be high, but this is only temporary.

Cultures of the wound should be made in all cases of suspected tetanus. The *Bacillus tetani* cannot always be demonstrated, and a negative culture does not rule out tetanic infection.

The presence of other organisms in wound cultures is important data, as certain bacteria inhibit and others help the growth of tetanus spores. Blood cultures are negative, as tetanotoxin has a special affinity for the central nervous system.

SPECIAL EXAMINATIONS.—The wound of suspected tetanic patients should always be examined by *x*-ray for the presence of possible foreign bodies of metallic origin. This should be a routine procedure, especially in gun-shot wounds of any type. In this routine procedure small pieces of bullet casings, fragments of bullets, etc., are commonly found, although the main projectile may have been removed.

Diagnosis.—The diagnosis of tetanus in the early stages is not always easy. To save the life of the patient early diagnosis is essential, for treatment with serum must be established before too much tetanotoxin has combined with the nerve-cells, and in order to prevent the fixation of subsequent toxins. When the toxin has entered the nerve-cells the value of antitetanic serum is questionable; hence, the importance of early diagnosis.

The diagnosis is made on the basis of the clinical history, a wound, especially of the extremities, an operative wound, or in rare cases even on the basis of a needle puncture followed by an incubation period of from two to twenty-one days or more. After this the development of the prodromal symptoms takes place as described above, followed by tonic or clonic spasms, trismus and the classical symptoms. Cultures from the wound showing the presence of *Bacillus tetani* or of spores confirm the diagnosis.

Well-marked cases following a wound cannot be mistaken for any other disease. However, the diagnosis should be made before the so-called classical symptoms develop.

In this early period the symptoms may be confused with strychnin-poisoning or tetany.

In *strychnin-poisoning* a history of the use of the drug, if obtainable, is important. The contractures of strychnin intoxication begin with clonic spasms, which quickly become tonic. The muscles of the jaw are never involved early, if at all. Between single paroxysms there is complete relaxation of the muscles, instead of a diminution in the degree of contraction, as in tetanus.

Tetany may cause more confusion in the diagnosis. The spasms of tetany are bilateral and symmetrical. They are chiefly confined to the muscles of the distal portions of the extremities. There is a peculiar involvement of the hands, which are conical in shape, the fingers extended as far as the interphalangeal joint but flexed at the ends. The thumb is flexed and tucked inside the fingers. The feet are semi-flexed at the ankle and the toes strongly flexed. Tetany occurs most generally in children, and is a symptom-complex manifested in constitutional toxemia more frequently than in metabolic pathology. If a wound is present with symptoms of tetany, cultures should always be made.

Complications.—*Lobular pneumonia* is the chief complication of tetanus. It occurs more frequently than is usually supposed. It occurs especially in cases with diaphragmatic and laryngeal spasm and in cases showing suffocation symptoms. It is usually fatal.

Cardiac dilatation occurs in some cases and is generally a terminal manifestation.

Classical tetanus is not associated with any other disease, except that it may be superimposed in sepsis from wounds.

Clinical Varieties.—In addition to the classical form of tetanus we have a few atypical forms in which the diagnosis may be difficult. These types have all been studied, a few of them reclassified during the period of the Great War. Many of the so-called atypical forms described in the past are now considered to be varieties of classical disease. For instance, the superacute forms are established and dependent upon the gravity of the symptoms immediately after their appearance. Splanchnic tetanus cannot be classified as atypical, for if the trismus does not become generalized it is only because death occurs within from twenty-four to forty-eight hours.

SIMPLE CEPHALIC TETANUS.—This is a rare form of tetanus following a wound of the head. The symptoms generally appear in two to twenty-two days and are very insidious in their onset. The wound at this period (if incubation is prolonged) may be entirely healed. Trismus and contractions are established unilaterally or bilaterally, and localized in the muscles of the face and in some cases in the cervical region also. Dysphagic, hydrophobic, or paralytic symptoms never occur in simple cephalic tetanus.

CEPHALIC TETANUS, ACCOMPANIED BY DYSPHAGIC OR HYDROPHOBIC SYMPTOMS.—In this type of the disease, trismus occurs unilaterally on the same side as the head wound. The patient complains of pain and contracture in the jaw of the side affected. The temperature rarely exceeds 100 or 100.5° F., the pulse is rapid, in ratio to the temperature, running between 100 and 120. The trismus remains unilateral for four to six days and is generally continuous. Pharyngeal spasms are established, giving rise to the dysphagic symptoms, which may increase until hydrophobic symptoms appear. Contractions of the muscles of the neck may be present, giving a cervical opisthotonos. Severe dyspnea may occur with the pharyngeal spasms and is a bad prognostic sign. If hydrophobic symptoms occur, generalization of the tetanus is frequent, and is almost invariably fatal.

CEPHALIC TETANUS WITH FACIAL DIPLEGIA OR HEMIPLEGIA.—This is a most frequent form of cephalic tetanus. It was first described by Rose in 1872. It occurs following a wound of the face in a region close to the facial nerve. Paralysis occurs on the side upon which the wound is located, or, if the wound is centrally located, it may occur bilaterally. This is considered a pathognomonic phenomenon in this type of tetanus. The wound is often situated at the root of the nose, at the upper or lower border of the orbit, along the malar region, or in fact along the branches of the facial nerve, especially the superior division.

The period of incubation varies in duration from two to twenty-two days, during which time the patient is free from all symptoms. The onset of the disease may be very sudden. The patient may complain of pain when he attempts to open his mouth, or upon pressure over the masseters. This is generally bilateral. It appears first on the side corresponding to the wound. Contractures of the muscles of the neck appear shortly after the trismus. They appear first upon the side corresponding to the wound, or bilaterally if the wound is centrally located. The contractures are tonic in character but may become spasmodic on excitation. These contractures extend with the progress of the disease to the muscles of the back, abdomen and limbs. If the pharynx, esophagus and diaphragm are involved, the prognosis is bad.

Facial Paralysis.—In classical tetanus facial paralysis is extremely rare; but in this form of the disease it is always present. It usually appears about the eighth day of the disease. Its character is that of a peripheral paralysis, except that the phenomena of contracture and paralysis occur in the same muscle. This is a typical sign in the facial paralysis of tetanus. This type of paralysis is toxic and may be compared to post-diphtheritic paralysis. It generally remains localized and disappears with the disease. If the paralysis is the first symptom of the disease, and occurs without contractures or trismus, it must be differentiated from (*a*) severance of the facial nerve, (*b*) central paralysis or possibly Bell's palsy. The accompanying fever is in no way diagnostic, but the pulse shows a rapidity out of all proportion to the amount of temperature. The diagnosis of this type of tetanus then rests on (1) the face wound, (2) the incubation period, from two to twenty-two days, (3) trismus on the wound side of the malar region, increased by motion or pressure, (4) paralysis and contracture in the muscles of the face, unilateral or bilateral.

The prognosis must always be determined by the progress of the disease and its early treatment. It may be fatal in three or four days. The more favorable cases extend over two or three weeks with recovery. The mortality is not over 50 per cent. The treatment is the same as for other forms of the disease. The localization of the infection should encourage, in addition, the injection of antitetanic serum about the wound and perhaps dressings of serum for the wound itself.

Cephalic Tetanus with Ophthalmoplegia.—This particular type has the same etiology as other forms, the factor of most importance being the location of the wound, which is generally situated in the orbitosuperciliary region. This region is very commonly the seat of wounds because of its exposed location. The eyelids and eyeballs may also be sites of the infection, as reported in several well-defined cases. The symptoms of cephalic tetanus with ophthalmoplegia may be bilateral or unilateral. In general they are unilateral, the eye on the side corresponding to the wound being first affected. The paresis is generally incomplete. The patient appears drowsy, the upper lid falling and hiding the cornea. If the patient desires to see he rolls his head back and wrinkles his forehead in an attempt to open the affected eye.

Physical Findings.—Upon examination of the movements of the eye or eyes affected, it is found that they are fixed in one position. Only a very slight movement, if any, is present. Pupillary symptoms are generally established simultaneously with the paresis and consist in a pinpoint contraction of the pupil with loss of light reaction. Examination of the fundus, in the majority of the cases, shows simple hyperemia without other changes. A few cases show a normal fundus. In the diagnosis of this type of tetanus one must eliminate several diseases:

(1) False ophthalmoplegia due to muscle-spasm must be considered. In this spasms are inconsistent, while paralysis is fixed. The field of fixation is normal in spastic strabismus, but limited in paralysis. This may be easily determined by mobilizing the head, placing the eye on the center of the field of vision and making the eye try to follow an object from the center to the periphery. The sound eye should be open.

(2) If no wound can be demonstrated, meningitis (cerebrospinal or tuberculous), with ocular palsy, must be ruled out. The prodromal symptoms—chills, headache, and mental disturbances—do not mark the onset of tetanus. Kernig's sign, high temperature and slow pulse are not present in tetanus. Lumbar puncture with chemical, bacteriological, and cytological examination should remove any doubt as to diagnosis.

(3) Wounds of the orbital region, with fractures of the orbit, may cause symptoms similar to those of paralysis. These symptoms are generally caused by hemorrhage back of the orbit, with sufficient pressure to fix the eye.

(4) Hysterical ptosis is accompanied by other signs of hysteria and is not permanent.

Prognosis.—The period of incubation is an important prognostic factor in this, as in all forms of tetanus. Ophthalmoplegia, apart from other tetanic symptoms, gives a good prognosis, for its duration is short, and it disappears with the onset of trismus and facial paralysis. Chronicity also gives a favorable prognosis. The treatment is the same as in all forms of tetanus.

Local Tetanus of the Limbs.—The forms of tetanus which are localized in a wounded part of the body and which at a later date show classical tetanus must not be confused with *local tetanus,* for this latter type is local during its entire course. There are two recognized forms of local tetanus, the *early* and the *late* forms. In the first-named variety, the incubation period is from five to ten days. In the second or late variety the period of incubation varies. It generally exceeds twenty days. Cases have been reported in which it lasted as long as seven months (Huntington). Late or tardy surgical operations may explain the long period of incubation in some cases. The spores may be nonvirulent and encapsulated by fibrous tissues. Re-operation such as reamputation, plastic bone operations, etc., may liberate these encapsulated spores. Since the resistance of the patient is lowered by the trauma of operation, local or general tetanus may develop.

Period of Incubation.—The early or prodromal symptoms of this type are most important. The patient usually complains of pain in or about the wound. These pains are shooting in character and may be described by the patient as rheumatic. The pains are accompanied by twitchings and muscular paralysis. They are most common in the limbs containing the wound. Therefore, pain in the wound, localized in a limb, without apparent cause, should arouse suspicion of tetanus.

These prodromal symptoms increase as the disease progresses and spasm of the entire limb or groups of muscles makes its appearance. At first the spasm is clonic in character, but later it becomes permanent. The limb is usually fixed in extension or in acute flexion, the muscles become board-like in their rigidity and it is not possible to move the limb.

Course of the Disease.—The face of the patient becomes anxious, especially during the period of the development of the disease. It is not the ***risus sardonicus*** of classical tetanus but an expression of anxiety. This is increased and made more apparent by the effect of external stimuli. Any noise, a bright light, moving of furniture about the room, or touching the bed, etc., cause spasm and pain. Percussion or palpation of the limb affected increase the rigidity and cause pain. The reflexes of the limb involved show marked increase.

Examination of the wound at this time may (in the late variety) show it to be completely healed; in the early type the appearance of the wound may be changed. Suppuration is generally diminished, granulation tissue has become arrested in its growth, the skin is increased in redness, and some dead tissue may be present.

The general symptoms are not at all typical. The patient generally shows some rise in temperature, but not to a very high degree—from 100° F. to 101° F. (37.8° to 38.3° C.). The pulse is more rapid, however, ranging from 100 to 120. The urine is generally diminished in quantity, and sweating is a frequent symptom. The respirations are but slightly embarrassed, if at all. Retention of urine is not an uncommon symptom.

The course of the disease is chronic. The first stage of painful contractions and fixation of the limb generally extends over a period of from ten to twenty days. The second stage then follows, in which the painful contractures cease but the limb still remains rigid and is fixed by the board-like rigidity of the muscles. This period lasts from twenty-five to forty-nine days. During this time, the muscles may become atrophied; tendon contractures, trophic ulcers, and vasomotor disturbances may become established. The third period, that of recovery, may be extended over a long time. From three to four months is not excessively long for this period of recovery.

Diagnosis.—This is made from the above enumerated symptoms. Certain conditions, however, must be eliminated, namely: (1) irritation of motor and mixed nerves, (2) spasmodic monoplegia accompanying cerebral or medullary lesions, (3) contractures due to diseases of bones or joints, and (4) tetany.

Prognosis.—In local tetanus of the limbs the prognosis does not depend upon the time of incubation, as in other forms; although the disease tends towards chronicity, death may occur. Reuter reported 3 deaths in 6 cases. Localized postoperative tetanus has a higher mortality than this form. Complications are more frequent in local tetanus, and orthopedic measures often have to be resorted to in order to restore function to the limb or limbs affected.

LOCAL TETANUS WITH PARAPLEGIA.—This is of extremely rare occurrence. Two forms have been described, however: a *superior paraplegic form* in which the hands, forearms and arms are flexed and rigid, and an *inferior form* manifested by fixation of the legs, thighs, and feet in extension by muscular rigidity. The prognosis is good; the few cases reported have recovered.

ATTENUATED TETANUS.—This is also a very rare form, which develops after a long period of incubation. The symptoms have a very gradual and insidious onset. Stiffness of the muscles of the wounded part or of the jaw characterizes its appearance and is accompanied by exaggeration of the reflexes. The facial expression is abnormal and anxious.

These patients show no constitutional symptoms. They are not incapacitated and are usually up and about. The prognosis is very good. The attenuated cases are probably due to the lengthening of the incubation period by prophylactic injections of sera.

Treatment.—The treatment of tetanus may be divided into two main considerations.

(1) Prophylactic treatment.
(2) The treatment of established tetanus.

PROPHYLAXIS.—The prophylaxis of tetanus needs no words as to its necessity and importance. Its value has been definitely established. The incidence and statistical proof are discussed in this article under Statistical Summary.

The prophylaxis must, of necessity, be both local and general:

Local treatment consists in the **cleansing** of **the wound,** general treatment in **antitetanic serotherapy.**

All wounds under suspicion must be cleansed early. This is of as great value in the prevention of the disease, as is the use of serum. Either general or local anesthesia should be used, depending upon the size, location, etc., of the wound. Whether the wound has been caused by the accidents of civil life or by a wound incurred in the war, the principles remain the same. Mechanical sterilization should take place by the removal of all traumatized tissue which has been devitalized (as muscle, congested in appearance, with loss of contractile power or stimulation), and all devitalized skin and fascia should be cleanly removed.

All dirt, clothing, pieces of bone denuded partially or completely of their periosteum, and foreign bodies of all kinds should be removed by clean-cut surgery, as they may be the nidus of Nicolaïer's bacillus and of other anaërobic bacteria.

During the Great War experience has shown us that extensive, mutilating surgery cannot accomplish more than to prevent further increase of toxins. Amputations, even in badly traumatized limbs, will not prevent tetanus and so should be discarded, unless indicated on general surgical principles.

The mechanical sterilization by surgery should be augmented by the use of antisepsis. **Tincture of iodin** applied to the wound will neutralize tetanic toxin but, even after its use, cases have been known to develop.

Oxygen.—**Peroxid of hydrogen, magnesium peroxid,** or **calcium peroxid** are of value as a dressing and are perhaps the best chemicals at our disposal for chemical sterilization of the wound. The tetanus bacillus, because of its anaërobic qualities, is killed by oxygen, and the gas, especially in its nascent state, cleanses the wounds, destroying toxins, detaching shreds of tissue, blood, pus, etc., without any harmful action on the tissues (Dutertre). The wounds should be irrigated with these solutions at least once daily, and wet dressings of the same applied.

Calcium hypochlorite and solutions of **bromin water** have been used, according to some writers, with good results. The author has had no experience with them, and prefers the peroxids. Desiccated and powdered **antitetanic serum** has been used as dressing for wounds and is about of equal value with the application of diphtheritic toxin to diphtheritic membrane.

Ultra-Violet Rays.—Treatment by means of the ultra-violet rays is an effective means of killing the spores and toxin in a wound. Experimentally, at least, tetanic bacilli spores are very susceptible to the violet rays.

The rays cause an inflammatory reaction in the wound, producing hyperemia with cellular exudation and increase of oxygen of arterial origin. It may be said to be of no small value, and a good method of treatment.

Even although mechanical and chemical sterilization, as described, has been carefully carried out, it is a fact that cases of tetanus will sometimes develop. It then becomes necessary to protect the individual against the disease by the injection of antitetanic serum.

Serotherapy.—As the immunity to tetanus lasts from seven to eight days after an initial dose of 10 c.c. (French or American) serum, one injection is not sufficient. In the author's service with the American and French armies in France, it was a standing army order that the wounded should receive 10 c.c. serum subcutaneously as soon after the wound was received as possible (First-aid Station) and a second dose of 10 c.c. within a period of ten days from the time of the wound. This was routine in all cases of wounds, gas burns, and trench feet.

It is best to give this serum subcutaneously, about ½ to 1 c.c. being injected, and then to wait three or four minutes for possible reactions before injecting the full dose. Aseptic precautions are essential. The favorite localities are the subcutaneous tissue of the flank of the abdomen, the thigh, or the scapular region.

It is needless to add that prophylaxis as indicated above should be carried out as soon as possible after the wound has been inflicted.

Children may be given one-half the adult dose, or 5 c.c. of serum, according to age.

When any surgical procedure is contemplated on a patient who has had a suspicious wound, even if the wound has healed and a period of from one to three months has elapsed, a prophylactic dose of serum should be given before operation.

The curative treatment of tetanus may be divided into:

(1) General management.
(2) Local surgical treatment of the wound.
(3) Symptomatic treatment.
(4) Antitoxin therapy, including specific serum therapy.

GENERAL MANAGEMENT.—Patients with tetanus should be isolated in a **quiet, dark room** and kept **free from reflex irritations.** Everything should be done to promote the rest and quiet of the individual. Care should be taken that other patients are not infected from wound discharges as tetanus is infectious.

Diet.—Patients with well-developed or severe tetanus cannot be fed by mouth. In such cases a **nutrient enema** must be resorted to, which can be augmented by the use of enemas of a 7-10 per cent. aqueous solution of **glucose.** A 5 to 10 per cent. solution of **sugar** can also be given intravenously.

To those patients who do not show any difficulty in swallowing, liquids may be given by mouth. **Solid foods** should **not be given** because of the spasm of the muscles in deglutition, caused by the irritation of food particles.

Bathing.—Many patients experience great relief from **warm baths** given twice daily. They seem to have a decided calming effect and to diminish the trismus. The bath is started at a temperature of 97° F. (36.1° C.) and increased to from 106° to 108° F. (41.1° to 42.2° C.).

Urine.—As the toxins are eliminated by the kidney the urine should be watched, and **fluids forced.** Retention of urine is not uncommon in cases with severe trismus.

Bowels.—Constipation is the rule in tetanus and may become severe.

SYMPTOMATIC TREATMENT.—After the development of general symptoms, treatment should be directed toward alleviating these, and giving the patient as much **sleep, rest,** and **quiet** as possible. Rest and sleep, if they can be induced, are a great factor toward recovery. The **sedative** and **narcotic drugs** found to be of most value are chloral, chloretone, morphin, sulphonal and chloroform. Chloral hydrate and chloretone are the most effective.

The patient with general symptoms should be given **chloral hydrate** in large doses, starting with from 20 to 30 grains (1.3 to 1.95 grams) by mouth every four or five hours and increasing the dosage until the full physiological effect is reached, or the convulsions and muscle-spasm have stopped, or have at least become less severe. Chloral is well borne in tetanus cases.

If the patient shows hydrophobic symptoms, laryngeal, or pharyngeal spasms, the drug should be given per rectum in greater quantities. **Chloretone** may be used instead of chloral, as it has shown its value in the treatment of such cases. It is frequently used at night to produce sleep, and to allay spasms. A satisfactory manner of administering this drug is to give from 40 to 47 grains (2.60 to 2.93 grams) in olive oil per rectum. This may be repeated each evening as long as is necessary.

Morphin sulphate grain 1/8 (0.008 gram) **subcutaneously** should be used to allay pain. In adults grain 1/8 every four hours is effectual. If there is much dyspnea, or diaphragmatic disturbance, the dose of morphin should be guarded, because of its effect upon the already embarrassed respiratory system. Cyanosis, unless marked, is no contraindication to its use, as all cases of general tetanus show cyanosis.

In severe cases of classical tetanus, when the diaphragm and larynx are involved, with fast-recurring convulsions, **magnesium sulphate** should be used **intraspinally**. This drug produces rapid and prolonged relaxation. The relaxation sets in in half an hour and lasts for varying lengths of time up to twenty-four hours. It should be repeated when necessary and the dose gradually increased, if the desired effect is not produced. Magnesium sulphate has not shown curative or specific value in the treatment of tetanus, but it has a very high value in stopping the convulsions and thus allowing rest. The dose of magnesium sulphate is important, as this drug is not free from danger. There can be no hard and fast rules for its dosage. It is best to start with a small but effectual dose and to increase it until the desired results are obtained. There is danger of producing respiratory paralysis by the use of the drug. In interpreting the result of this drug the respirations are of more importance than cyanosis, as all tetanus cases show some cyanosis. If opisthotonos is present and frequent spasms, a very light **chloroform anesthesia** should be used for the spinal injections. The chloroform should be discontinued immediately after the withdrawal of the needle.

The needle is introduced into the spinal canal, under aseptic precautions, with the patient lying upon his side. If the spinal fluid is under pressure, it is allowed to flow until the pressure has somewhat diminished. One c.c. of a 25 per cent. solution of magnesium sulphate for each 10 kg. of the body weight is slowly injected into the canal. The patient is then kept in the horizontal position with the head slightly raised. If the patient should show signs of respiratory paralysis, the spinal canal should be washed out with **saline solution** and a subcutaneous injection of **calcium chlorid** given. There is very little or no danger if the drug is properly given. The author has never seen any untoward results from its use. Wentrand, Madelung, Kocher and Stadler report brilliant results with the drug.

Magnesium sulphate was widely used by the Germans during the late war and to a lesser extent by the French and English. In children ½ c.c. for each 9 kg. body weight is a safe dosage, depending upon age and weight.

If one is not familiar with the technic of spinal puncture or if circumstances are such that it cannot be used, the drug may be given subcutaneously. From 12 to 16 c.c. of a 25 per cent. solution may be given. It is generally necessary to repeat this dose three times per day, for the first twenty-four hours, in order to obtain the desired result.

Three or four injections are usually sufficient.

These drugs and their usage are purely symptomatic and of no curative value except indirectly, by insuring rest for the patient. They are used in conjunction with antitetanic serum, which is discussed below.

SURGICAL TREATMENT.—If intraspinal injections fail in an acute case, surgical exposure of the nerve-trunks, especially of the limbs, is indicated, with injections directly into the nerve-sheaths. (Endoneural injections.)

ANTITOXIC TREATMENT.—*Phenol Treatment.*—The phenol treatment of Bacelli (1888) should be mentioned. It is undoubtedly of some value. During the war it was extensively used in the Italian Army, with encouraging results. The author has seen it used in a few cases by the French surgeons, but always combined with the use of antitetanic serum.

Patients with tetanus seem to have a tolerance for phenol. Its action is to neutralize the toxins and to diminish the reflex excitability of the spinal cord through its analgesic properties. Phenol is best given subcutaneously in a 2 to 3 per cent. solution in olive oil. It can be given at from one to three hour intervals in a dosage of from 1 to 1.5 grams every twenty-four hours. The injections may be continued for several days, fifteen to twenty days if necessary.

Antitoxic Serum.—The antitoxic power of serum was first demonstrated by Kitasato and Behring in 1890. In 1892 Villard showed that the *Bacillus tetani* will produce toxin in the sera of protected animals and also that the bacillus grows and multiplies in the tissues of protected animals, proving the serum to be antitoxic but not germicidal in its action.

In 1893 Roux and Villard demonstrated that the immunity acquired from injections of serum was immediate but lasted only from seven to eight days.

Experimentally, if an animal is given a subcutaneous dose of antitetanic serum and after an interval of one hour is given a lethal dose of tetanotoxin, tetanus does not develop and the animal survives.

If the serum and the toxin are injected simultaneously at different points, the toxin is absorbed faster than is the antitoxin. The toxin which is not neutralized causes mild local tetanus, which is almost always curable.

As has been stated, the immunity is temporary only, as the antitoxin is soon eliminated. The spores inhibited by phagocytes and by the serum again develop, producing the toxin, which poisons the organism at a time when no antitoxin is present to neutralize the toxin, and tetanus develops.

The proof of this data has been established by Nocard. He observed that animals are frequently infected with tetanus through wounds or operations. Of 2,500 animals given prophylactic injections immediately before operations, none developed tetanus. Of 6,000 other animals given injections from one to four days after operation, 1 case of tetanus developed. During this same period he observed 315 cases of tetanus in animals which had not received prophylactic injections. In 1915 Brazy reported that of 200 wounded, 100—without selection—were given preventive injections. None contracted tetanus. The remaining 100 in the same group under the same conditions, who were not injected, developed 18 cases of tetanus. This seems rather striking evidence of the protective powers of antitetanic serum.

Antitetanic serum is the one curative agent of proven value in the treatment of tetanus. We have the subcutaneous, intravenous, intramuscular, intraspinal, and endoneural routes by which to administer the serum. There is no absolute data in the literature proving any one of the routes to be the most effectual.

In severe cases with diaphragmatic or laryngeal spasm and severe, frequent convulsions, and in the acutely sick, the *intraspinal* is the method of choice, combined with the *intramuscular* or *subcutaneous* routes. The serum should be given as soon as the diagnosis is made, as time is a very important factor. Worslert and Drought report the successful treatment of a severe case lasting nineteen days, which was given 146,000 units of antitoxin. In the attenuated forms appearing after long incubation periods, and in most cases of local tetanus, the subcutaneous or intramuscular route is indicated, with local injections about the site of the wound.

In acute cases with trismus the following plan of dosage, published by the British War Office Committee for the curative treatment of tetanus, may be of value for general use:

Day	Subcutaneous	Intramuscular	Intrathecal
1	—	8,000 units*	16,000 units
2	—	8,000 "	16,000 "
3	—	4,000 "	8,000 "
4	—	4,000 "	8,000 "
5	—	2,000 "	—
6	—	2,000 "	—
7	—	2,000 "	—
8	—		—

*Forty U. S. A. units are equivalent to one German unit. The U. S. unit of antitoxin is ten times the least amount of serum required to preserve the life of a 350 gram guinea pig for ninety-six hours when the former is mixed with the official test quantity of standard toxin (100 minimum lethal doses) and injected subcutaneously. Commercial ampules of sera usually contain about 1,500 U. S. units in about 10 c.c. of serum, or can be procured in a more concentrated form for spinal use.

French sera are less concentrated than the U. S. or German sera, as their unit has less strength.

If opisthotonos is present, with severe trismus, the spinal puncture should be done under **chloroform anesthesia.** It is best done in the horizontal position. From 10 to 20 c.c. of spinal fluid are allowed to flow out, and the serum allowed to run in either by gravity, through a glass container such as the barrel of a 30 c.c. glass syringe with tube connections, or gradually forced in with a syringe. The gravity method is preferable. The high potency serum containing 800 units per mil is preferable for intraspinal use. These injections should be given early and daily until the symptoms subside. The intramuscular or subcutaneous injections need no description, as they are given in the same way as any other serum.

The dosage in local and attenuated forms of tetanus may be reduced to 10,000 units per day, at two day intervals, given by the subcutaneous or intramuscular route.

In cases of local tetanus, because of the tendency of the disease to localize in the wounded limb or some other region of the body, the author believes that local injections in the muscles about the wound should be given, in addition to the other injections.

In children the same treatment should be used, the dosage being regulated according to age and the same routes for injection used. The intravenous method of injection is not commonly used, as many writers consider it the most dangerous. The endoneural route has not been used to any extent in this country. Von Behring was the first to use it in the often quoted case of his laboratory assistant, who developed tetanus three times, and who was cured twice by the usual treatment. The third time his condition became critical and the endoneural method was used with success.

(*a*) *Serum Sickness.*—Accidents following injections of serum are few, but they do occur. This, however, should never prevent the physician from injecting serum in suspected or established tetanus. These accidents are best divided into two classes:

(1) Those following first injections.
(2) Those following re-injections.

From eight to fifteen days following the first injection the patient may exhibit an eruption, starting generally on the face and rapidly becoming generalized. The eruption is most frequently of an urticarial form, either of small maculæ or of large patches with rapid extension. Some cases show an erythema resembling scarlet fever. In some few cases the eruption is mixed, consisting of scarlatiniform erythema and urticarial patches. The urticarial is the most frequent form. Pain of the neuralgic or myalgic type occurs, especially in the legs and back. The temperature is elevated to 99°-101° F. (37.2°-38.3° C.). These reactions vary in severity in different individuals, usually lasting not longer than four days.

Occasionally the reaction is more severe, the temperature reaching 104° F. (40° C.), with delirium, headache, stiff neck and at times edema and albuminuria. The author has never seen a severe form of serum sickness. The milder forms were not infrequent in the case of American and French wounded during the war, occurring in about 10 to 15 per cent. of the cases.

A few fatal cases have been reported. These symptoms are explained by the well-known toxicity of the serum of any animal to an animal of another species. A heterogeneous, nonantitoxic serum causes similar phenomena.

(*b*) *Re-injection Symptoms.*—The re-injection symptoms are those of anaphylactic shock manifested by rapid collapse, with diminution of arterial pressure.* When a patient has suffered from sepsis or shows a pathological taint such as tuberculosis, hay-fever, asthma or a disposition to urticaria, and a re-injection is necessary, the anaphylactic method of Besredka should be employed, giving from ½ to 1 c.c., and after three to four minutes the necessary additional dose, if no reaction has occurred.

If such an accident should occur, the patient should be placed in a high Trendelenberg position, and **adrenalin** and **chlorid of calcium** administered, besides **external heat** and **stimulants.**

In observations of about 3,000 re-injections, the author has never seen any degree of anaphylaxis. It seems probable that the frequency of anaphylactic accidents has been greatly exaggerated. In innumerable re-injections during the war the incidence of anaphylactic shock was very low.

In summarizing the treatment of tetanus, the facts to be emphasized are:

(1) Prophylactic injections should be given to any patient who shows a wound contaminated by dirt, particles of clothing, splinters of wood, or metallic foreign bodies.

(2) Absolute rest, quiet, isolation and good nursing are essential for success.

(3) To prevent exhaustion from spasm and convulsions the sedatives, chloral, morphin, chloretone, magnesium sulphate, are of great value.

(4) Specific treatment with serum should always be given early and in massive doses by the intraspinal, intramuscular, subcutaneous or endoneural routes. To give serum and then wait for symptoms to indicate an increase in dosage is very poor practice.

(5) Local treatment of the wound is important; operative interference is not indicated after the disease is established, except in rare cases.

Prognosis.—The statistics of the mortality in tetanus, as reported in the literature of the last three years, has indeed become voluminous. The French, British and German reports show a marked decrease in the mortality rate, especially during the last eighteen months of the war.

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* Collapse in cases of anaphylactic shock appears within a few minutes, but passes off rapidly. The symptoms are those of shock and may include soft, rapid pulse, dyspnea, cyanosis, convulsive movements, low blood-pressure, pains in the limbs, back, and head, vomiting and diarrhea. The patient may become comatose. Death may occur immediately or in a few hours.

The last report of the British War Office shows a mortality of 19 per cent. In 1914, 57 per cent. and higher was reported.

A few clinical observations seem to be of the most value in determining the prognosis of this disease.

It is relatively true that the longer the incubation period the better the prognosis. Cases which have received prophylactic injections have a more favorable prognosis, as they show a longer incubation period and a greater tendency toward a localized tetanus.

The prognosis in local tetanus is generally good. The location of the muscle-spasms is an aid in prognosis. If the spasm is located in the peripheral muscles, even in the presence of opisthotonos and trismus, the prognosis is better.

Diaphragmatic and laryngeal involvement gives a bad prognosis, even if other muscles show no spasms. The same is true of cases manifesting hydrophobic symptoms.

High temperature and pulse-rate are unfavorable.

Tetanus following wound sepsis or in the case of a patient with multiple wounds usually gives an unfavorable prognosis.

In acute classical tetanus, if the patient survives the first four to six days of the disease, the chance of recovery is improved.

Lobular pneumonia is a complication which is more common than is generally thought and is usually fatal.

The development of pathological conditions in wounds demanding radical surgery increases the severity of the disease. The mode of death in tetanus may be by suffocation, exhaustion, toxemia, pneumonia or cardiac dilatation.

Pathology.—*Bacillus tetani* and its spores always remain at the site of the wound, generally in company with other pathogenic bacteria. The bacillus never invades the blood stream or parts of the body distant from the wound.

By its metabolism, the bacillus of tetanus produces one of the most poisonous substances known to the human organism—tetanotoxin. The exact nature of this toxin is not known. It resembles the diastases. The diffusion of the toxin is very rapid; it is absorbed by way of the peripheral nerve-filament and travels along the axis cylinders to the nerve-centers, where it becomes fixed by the nerve-cells. A portion of the toxin enters the circulation. The disease does not manifest itself until sufficient toxin is produced to cause the nervous symptoms.

Antitoxin cannot neutralize toxin fixed by nerve-cells. It is limited in its antitoxic action to that part of the toxin which has not been fixed by the nerve-cell but is still free in the blood and lymph or at the site of production in the wound.

MORBID ANATOMY.—The postmortem findings in tetanus are very meager. The blood-vessels show an overfilling with cellular exudate in the perivascular spaces.

The ganglion-cells of the spinal cord may show chromatolysis.

The *Bacillus tetani* may be demonstrated in the pus from the wound. The negative findings in the tissues are of pathological importance.

Statistical Summary.—The statement of Hippocrates that: "such persons as are seized with tetanus die within four days, or if they pass these they recover" gives some idea of the attitude of the ancients toward this disease.

In reviewing the statistics of the Great War and of some of the previous wars occurring before the discovery of tetanus in 1883 and, subsequently, of the antitoxin of von Behring, one is struck by the lack of difference in the prognosis and incidence of tetanus.

It is only in 1916-17 that an appreciable lowering of the incidence and mortality has been accomplished by rigid prophylaxis and massive doses of serum given on *early* diagnosis.

In the Crimean War the British report shows 12,094 wounded with only 9 cases of tetanus, giving 1.5 per thousand. In our Civil War 246,172 wounded are reported, with 505 cases of tetanus, giving a little over 2 per thousand.

In the Franco-Prussian War 95,000 wounded are reported with 350 cases, showing an incidence of 3.5 per thousand. The very low incidence of 1.2 per thousand is reported from the Russo-Turkish War (1877-1878) among 51,700 wounded.

The exact incidence of tetanus during the Great War is not at this time known. Isolated reports of different observers vary greatly.

In September, 1914, the British reported 16 per 1,000. In November of the same year the rate had fallen to 2 per thousand. Two German reports, one by Madeling, gives 6.6 per thousand, another, from a different base, by Kummell, from 6 to 6.5 per thousand. Couteand reports 58 cases among 60,000 at Cherbourg, Brazy in 1914 reported 4.18 per thousand among men receiving prophylaxis and 12.79 per thousand where injections were given only in suspicious cases.

This high incidence can be attributed to the lack of preparation, organization, and of serum in the early days of the war, and to the contaminated soil of France and Belgium.

It is with more encouragement that we turn to the prognosis and mortality.

A report by Surgeon-General Sir David Bruce of the War Office Committee for the study of tetanus presents the mortality of a representative number of cases more accurately than it can be described.*

Years	No. of Cases	Recovered	Died	Mortality
1914–15................	231	98	133	57.6 per cent
1915–16................	195	99	96	49.2 per cent
Aug. to Oct., 1916.......	200	127	73	36.5 per cent
Oct. to Dec., 1916.......	100	69	31	31.0 per cent
Dec., 1916 to Mar., 1917.	100	81	19	19.0 per cent

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* **Cases treated in Home Hospitals.**

In the first year of the war 47 per cent. of the cases had a short incubation period; in the last reports this had fallen to 10 per cent. Also the cases with long incubation periods had risen from 6.4 to 69 per cent.

Four principles of treatment established by experience during the war in the treatment of tetanus are responsible for this encouraging fall in the death-rate:

(1) Proper dosage of prophylactic serum.
(2) Better surgical treatment of wounds.
(3) Early diagnosis.
(4) Larger therapeutic doses of serum.

Distribution.—According to Anders and Morgan, tetanus in this country is most frequent in the Hudson Valley, Long Island and the Atlantic States. Fourth of July tetanus has almost ceased to exist, due to proper prophylaxis.

In some of the foreign countries it is much more common. In Belgium and France the incidence has been high during the war. The Islands of Jamaica and Cuba show it to be five or six times more frequent as a cause of death in children than it is in the United States.

In England the disease is not common but has increased of late years, even before the war.

St. Kilda, one of the islands of the Western Hebrides, has shown a very high percentage of cases in children and infants.

BIBLIOGRAPHY

Antherson, J. F. Public Health Report U. S. Marine Hosp. Service, Wash., 1908, xxiii, 857-861.

Ashurst, John. Rational treatment of tetanus. Amer. Jour. Med. Sc., June-July, 1913, pp. 77-117.

Bacri. Traitement du tétanos confirmé par le sérum antitétanique à doses massives et répétées. Bull. Acad. de méd., Paris, 1915, xxiii, 381-383.

Bazy, M. Note sur les réactions après l'injection de sèrum antitétanique. Bull. Acad. de méd., Paris, 1916, lxxvi, 216-220.

——— Note statistique sur le tétanos. Gaz. méd. de Par., 1915, xxxvi, 4.

——— Statistical remarks on tetanus. Med. Press and circ., 1914, clix, 794-798.

Berard, L., and Tumiere, A. Sur le tétanos tardiff. Bull. Acad. de méd., Par., 1915, lxxiv, 234.

——— Sur la durée de l'immunité conférée par les injections de sèrum antitétanique. Bull. Acad. de méd., Paris, 1916, lxxv, 666-668.

——— Études sur le tétanos. Lyon clinic, 1914-1915, xii, 404-408.

Bruce, Sir David (Surgeon-general). Tetanus treated in home military hospitals. An analysis. Lancet, June 30, 1917, pp. 986-990.

——— Brit. Med. Jour., 1915, ii, 593.

——— Brit. Med. Jour., 1917, i, 48-118.

——— Lancet, 1916, ii, 929.

——— Lancet, 1917, 1, pp. 680-986.

——— Lancet, 1919, ii, 411.

——— Journal Roy. Army Med. Corps, Lond., 1915, xxv, 534-545.

Courtois, Suffit and Giroux, R. Abnormal forms of tetanus. In: Medical and surgical therapy. Vol. I, 708-927.

——— Les formes anormales du tétanos. Paris, Masson, 1917.

Couteand. Quelques formes anormales du tétanos. Bull. et mém. Soc. de chir. de Par., 1916, xlii, 370-381.

Dean, H. R. Lancet, May 5, 1917, p. 673.

——— A report on twenty-five cases of tetanus. Lancet, May 5, 1919, pp. 673-680.

Delafield and Prudden. Textbook of pathology, 1919.

Faber, Knud. Berl. klin. Wchnschr., 1890, No. 31.

Greenwood. Lancet, 1917, p. 966.

Hull, Alfred J. Surgery in war (second ed.), 1919, pp. 103-127 (Browning).

Kolle and Wassermann. Handb. d. path. Mikroörg., 1920, iv, p. 737.

Leishman and Smallman. Lancet, 1917, i, 131.

MacConkey. Brit. Med. Jour., 1914, ii, 609.

——— *Ibid.*, 1915, ii, 849.

Morris, G. W. Tetanus, a study of fifty severe cases from the records of the Pennsylvania Hospital. Phila. Med. Jour., 1903, lx, 835-838.

Nicoll. Jour. Am. Med. Assn., 1915, lxiv, 1982.

Osler, Sir W. Practice of medicine, 1915.

Roclu. Serum antitétanique et accidents sériques. Paris Med., 1915, pp. 450-456.

Roux, E., and Vaillard, L. Contribution à l'étude du tétanos. Ann. de l'Inst. Pasteur. Paris, 1893, vii, 65-140.

Sanford, A. H. Tetanus and the war. A review of the literature. Internat. Assn. Med. Mus. Bull., Wash., No. VII, 365-395.

Von Behring, E. Aetiologie, Prognose und Therapie des Tetanus. Schmidts' Jahrb., 1915, cccxi, 1-8.

CHAPTER XLIII

ROCKY MOUNTAIN SPOTTED FEVER

BY LUNSFORD D. FRICKS, M.D.

Definition, p. 49—**Etiology**, p. 49:—Mode of transmission, p. 49; Causative agent: the microörganism, p. 50; The virus vector, p. 51; Life history of Dermacentor andersoni, p. 51; Prevalence, p. 52; Seasonal occurrence, p. 52; Variations in virulence of strains, p. 52—**Symptomatology**, p. 53:—Prodromal period, p. 53; Symptoms during progress of disease, p. 53—**Diagnosis**, p. 54—**Treatment**, p. 56:—**Prophylaxis**, p. 56:—Tick eradication, p. 56; Prevention of infection, p. 57—General measures, p. 57; Serum therapy, p. 58—**Pathology**, p. 58—**Historical summary**, p. 59—**Geographical distribution**, p. 60.

Definition.—Rocky Mountain spotted fever is an acute, endemic, noncontagious, febrile disease transmitted to man accidentally by the bite of an infective wood tick. It is characterized clinically by headache, muscular and joint pains—most pronounced in the back and extremities—a continuous, moderately high fever and a petechial eruption appearing first on the ankles, wrists, forehead and dependent parts of the back and, thence, usually spreading over the entire body.

Etiology.—MODE OF TRANSMISSION.—The accidental inoculation of Rocky Mountain spotted fever virus through the bite of an infected wood tick (dermacentor) causes Rocky Mountain spotted fever in human beings. Man, however, plays no part in the perpetuation of the virus, and in this respect, the rôle of the infected person differs entirely from that played in malaria, yellow fever and exanthematous typhus. The virus of Rocky Mountain spotted fever is propagated in nature: first, by means of infected ticks feeding on and thus infecting susceptible animals, while these infected animals transmit the infection to other feeding ticks; second, through the hereditary transmission of the virus from an infected female tick to her eggs, and thence through the different stages of their development to a part of her progeny.

At least eight species of small wild animals found in the Rocky Mountain region are susceptible to infection with Rocky Mountain spotted fever virus, and these vary in importance in perpetuating the infection in different localities, in proportion to their abundance and their selection as tick hosts. These animals are the Columbian ground squirrel (*Citellus columbianus*), the pine squirrel (*Sciurus hudsonicus*), the yellow-bellied and the white-bellied chipmunks (*Eutamias luteiventris* and *Eutamias quadrivittatus umbrinus*), the woodchuck (*Marmota flaviventor*), the side-striped ground squirrel (*Callospermophilus lateralis* *cinerascens*), the badger (*Taxidea taxus*), the white-tailed jack-rabbit (*Lepus campestris*), and the cottontail rabbit (*Sylvilagus nuttalli*).

The larger wild and domestic animals of the region are generally immune to infection. Young horses have been infected by blood inoculations, according to Ricketts, but cattle, sheep, goats and old horses have frequently proved refractory to inoculations of 5 c.c. or more of blood from infected guinea pigs. Man, rhesus monkeys, guinea pigs and white rats (*Mus norvegicus albinus*) are highly susceptible to infection; domestic rabbits can be infected, while white mice (*Mus musculus albinus*) are immune to infection with the virus.

No biting arachnid other than the dermacentor and one closely related tick, and no biting insect has been found capable of transmitting the virus. Certain ticks of the species, *Dermacentor andersoni, Dermacentor modestus, Dermacentor albipictus* and *Dermacentor occidentalis,* have been found infected in nature, and eastern ticks of the species *Dermacentor variabilis* and *Amblyomma americanum* Linnæus have been infected experimentally. The transmission of the virus by a tick bite is not mechanical, since a tick once infected usually remains infective during life; the virus multiplies in the tick and the female tick transmits it to her progeny. Attempts made to infect fowl ticks (*Argas miniatus*) and *Ornithodorus coriaceus* by feeding on infected animals have failed; likewise such biting insects as the stable fly, bedbug, the common monkey lice and guinea pig lice of the laboratory are not infected by feeding on infected animals. The virus, however, will live for a longer period in the body of a bedbug than it will *in vitro* at room temperature. The virus may be propagated indefinitely without loss of virulence in susceptible animals, by the intraperitoneal inoculation into a fresh animal of from one-half to one c.c. of heart blood taken from the infected animal at the height of the disease. In guinea pigs, transfers from infected to fresh animals should usually be made at weekly intervals, while in monkeys the proper period for transfer is somewhat longer, approximating ten days. The virus in infected blood is rapidly destroyed when kept *in vitro* at room temperature, but when placed in a refrigerator the loss of virulence, though irregular, is decidedly slower. The virus will not pass through an ordinary Berkefeld filter under moderate pressure. The infectiousness of the virus is destroyed by heating at 50° C. (122° F.) for twenty-five minutes, but is not destroyed by rapid freezing; it is also lost after complete desiccation, requiring 24 to 36 hours. The virus cannot be thrown down from infected blood or serum even after rapid and prolonged centrifugation when undiluted, but when diluted ten times with normal salt solution this is easily accomplished. Rocky Mountain spotted fever in man and in laboratory animals is followed by pronounced and prolonged immunity.

CAUSATIVE AGENT: THE MICROÖRGANISM.—The causative agent in Rocky Mountain spotted fever infection has not yet been definitely identified. Unquestionably it is a living organism capable of multiplication both within certain ticks and certain warm-blooded animals, while it is incapable of growth in other ticks, biting insects, or closely related animals. Wilson and Chowning, in 1902, described a piroplasm in the red blood-cells of Rocky Mountain spotted fever cases, but subsequent workers have failed to confirm their findings. Ricketts reported the finding occasionally of diplococcoid and lanceolate, chromatin-staining bodies in fresh blood-smears stained with Giemsa stain and many small bacilli in infected tick eggs. These he believed to be different forms of a specific organism. The writer in 1916, in a recently isolated strain of Rocky Mountain spotted fever, reported finding small double granules and protozoan-like bodies in diluted blood centrifuged for six hours. Wolbach has described a red-staining lanceolate bacillus, a smaller rod-like form staining blue and a minute oval coccoid form found in endothelial cells of the smaller blood-vessels in mammalian hosts and in infected ticks.

THE VIRUS VECTOR.—Wilson and Chowning, in 1902, advanced the theory of tick transmission of Rocky Mountain spotted fever, which had previously been suspected by some of those familiar with the disease. Ricketts, in 1906, demonstrated that the virus is transmitted by the bite of an infected dermacentor tick, although, in 1905, McCalla and Brerton, of Boise, Idaho, infected two individuals by the bite of a tick removed from a Rocky Mountain spotted fever patient. (This experiment, however, was not reported at the time and has not been repeated.) As a result of further research work which has been done on the transmission of the virus, Ricketts' findings have been definitely confirmed and the dermacentor ticks of the Rocky Mountain region have been established as the carriers of Rocky Mountain spotted fever virus under natural conditions. The percentage of infective ticks in nature, as determined by collecting adult ticks from territory known to harbor the infection, and feeding them in groups upon guinea pigs, is extremely small. In three experiments involving 2,265 ticks, 8—or 1 in every 283—were found capable of infecting the guinea pigs on which they fed. Observations made of persons infected in the localities from which these ticks came, seem to indicate a much higher percentage of tick infection. Many instances have been reported of persons visiting these localities and being infected by the first tick bite. Estimates of a 10 per cent. infection among ticks, based on the frequency of human infection following tick bites in certain endemic areas of infection, are not unusual or apparently unwarranted. In view of the difficulties attending feeding experiments as conducted for the determination of infected ticks in nature, it is hardly wise to ignore entirely the common observation of more frequent infections among human beings following tick bites.

LIFE HISTORY OF DERMACENTOR ANDERSONI.—Adult male and female ticks commonly live for two years without feeding and may live longer, lying dormant under logs and stones during the winter. With the advent of the first warm days of spring these adults crawl up the grass, weeds and low bushes, from which they can more easily attach themselves to a passing host. As summer advances they become less active, ordinarily refusing to feed in hot weather. The larger domestic, and wild animals, including jack-rabbits, serve as hosts for the adult tick, and while feeding on them the sexes mate. The female becomes greatly engorged, then drops to the ground to lay thousands of eggs. The male tick may remain on the host to fertilize other females, after which he dies. The fertilized female usually begins egg laying within a few days after leaving her host and within a month these eggs should hatch into minute larvæ or seed ticks, usually appearing in June. The latter soon crawl up the most convenient herbage and wait for a small animal host. To this they attach, engorge in a few days, then drop off and moult into medium-sized asexual nymphs, which repeat precisely on similar hosts, usually the next season, the process of attaching, feeding and moulting previously undergone by them as larvæ. After moulting, the nymphs appear as adult male or female ticks.

Weather and food conditions pronouncedly affect this tick cycle by lengthening or shortening the period of time consumed in any stage of development, and winter may intervene between the different stages. The average time consumed in completing this life cycle in dermacentor ticks is two years. The eggs and larvæ are decidedly less tenacious of life than are the nymphal forms and adult ticks.

PREVALENCE.—Rocky Mountain spotted fever is intimately associated with the settlement and agricultural development of any locality which harbors infective ticks. The history of such localities has usually shown that cases of Rocky Mountain spotted fever first increase from year to year, and then decrease as the community passes through the various phases of grazing and agricultural development.

The greatest number of Rocky Mountain spotted fever cases reported from the entire region involved in any one year has never amounted to as much as one thousand. The average number in recent years has been approximately 500, but perhaps 750 cases annually more nearly represents the actual number of cases occurring, about one-half of which have been reported from Idaho. The greatest number of cases reported from Idaho in recent years was 380 in 1908, and 360 in 1915. Since then, however, a notable reduction has occurred in the southeastern part of the state, due to the reclamation and irrigation, for farming purposes, of lands previously tick infested. There is every reason to believe that the total number of cases occurring each season will gradually decrease in years to come. New areas of infection will develop in the future, it is true, but the shrinkage of present endemic foci will more than offset the spread into new localities.

SEASONAL OCCURRENCE.—The great majority of cases of Rocky Mountain spotted fever occur during the so-called tick season, that is, the time during which adult dermacentor ticks actively feed—from the first spring days to early summer. But, following the snow line, ticks will feed throughout the summer months and cases of Rocky Mountain spotted fever have been contracted in the higher mountains occasionally as late as August. When well warmed by sunshine or artificial heat, wood ticks may attach themselves even during midwinter, and a few cases of the disease have been observed under such unusual circumstances.

VARIATIONS IN VIRULENCE OF STRAINS.—Two different types of Rocky

Mountain spotted fever are commonly recognized clinically, depending upon the severity of the disease and particularly upon the mortality rate. These types are known as the *Bitter Root strain* and the *Idaho strain*. In the former the mortality rate among adults is nearly, if not quite, 90 per cent., in the Bitter Root Mountains of Montana; while in the Idaho strain it does not reach 5 per cent. This difference in severity has been constantly observed since the disease was first recognized and, in the beginning, added considerably to the perplexities of differentiating Rocky Mountain spotted fever from other diseases. Generally speaking, the Idaho strain prevails in the southern part of the infected region, consisting of the dry sage brush plains of the Snake River Valley in Idaho, in northern Utah, Nevada, and south-central and southeastern Oregon. All of this region is dry and hot during the summer months and there the jack-rabbit plays a prominent part as host of the infected ticks.

The mortality rate is higher throughout the northern part of the infected region, except in the Big Bend country of Washington, where the flora and climatic conditions more closely resemble those found in the south. In Colorado, Wyoming, and Montana the mortality rate approximates 20 per cent., while in the Bitter Root Mountains of southwestern Montana and northern Idaho, it is exceptional for an adult to recover from the disease. This country is severely cold during the winter, the temperature frequently remaining below zero for days. The summers, however, are mild and the tick-infested localities are generally shaded and moist. The jack-rabbit plays no part as host of the Bitter Root strain; the larvæ and nymphs commonly feed on Columbian ground squirrels and the adult ticks attach most frequently to the domestic animals.

No sharp line of demarcation exists, however, between the two types or strains of the disease. The strains gradually merge into each other clinically, and cases of the most severe type may be found in Idaho as well as Montana. The difference in the virulence between the two strains is noticeable in experimentally infected animals by the difficulty encountered in establishing the Idaho strain. The identity of the virus is shown, however, by specific cross-immunity. Perhaps the matter of greatest practical importance connected with the two clinically different strains of Rocky Mountain spotted fever is its bearing upon the prognosis of a given case.

Symptomatology.—PRODROMAL PERIOD.—The prodromal and early symptoms of Rocky Mountain spotted fever are similar to those observed in other acute, eruptive, febrile diseases and, as in these, vary in degree.

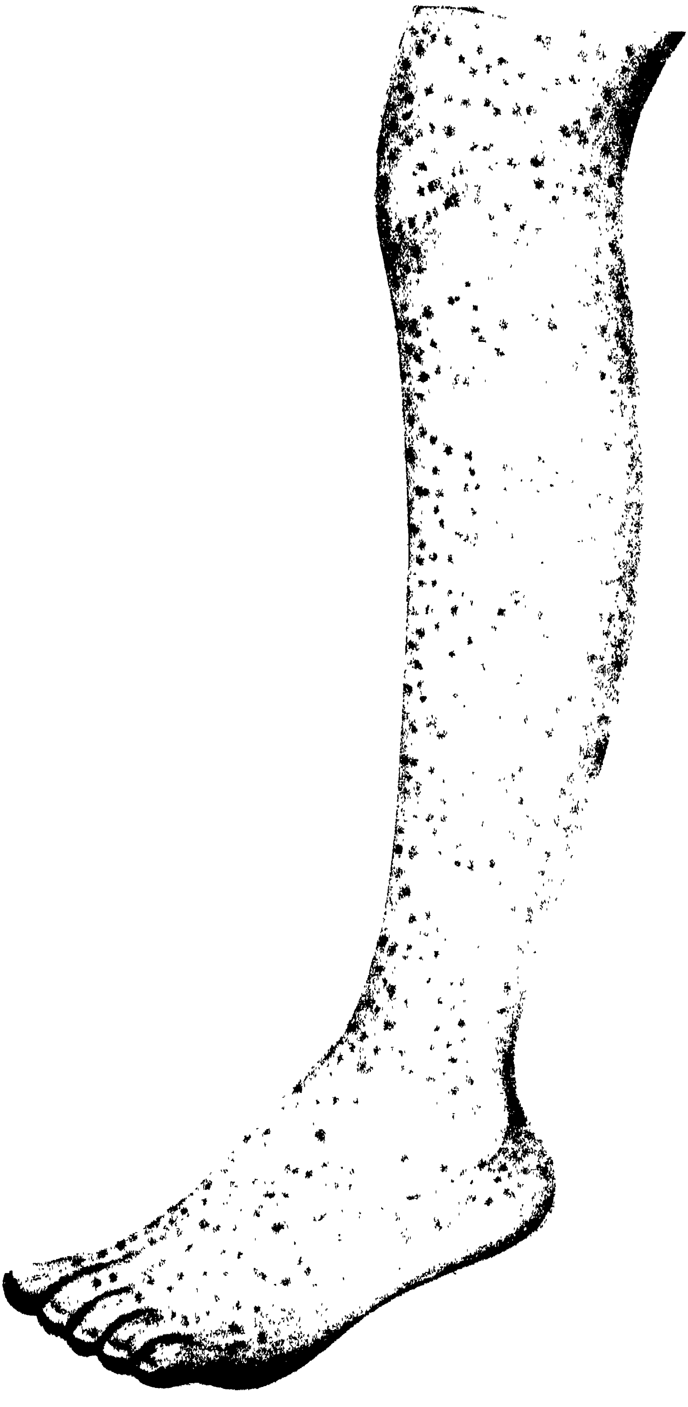
SYMPTOMS DURING PROGRESS OF DISEASE.—A short prodromal period lasting two or three days, during which the patient complains of malaise and chilly sensations, is usually followed by a distinct chill, pronounced headache and intense soreness in the muscles and bones. Photophobia and hyperesthesia are generally pronounced throughout the course of the disease. A macular, roseolar eruption on the face, neck, and upper thorax, though not always present, is frequently seen as early as the second day. The characteristic petechial eruption on the forehead, wrists, ankles and dependent parts of the back appears from twenty-four to forty-eight hours later. This eruption is first rose-red in color, rapidly passing to a dark blue, and, being the result of hemorrhages from the small blood-vessels, does not disappear on pressure. In severe cases the petechiæ increase in size, become purpuric and are accompanied by extensive sloughs on dependent parts of the body. In human cases sloughing of the soft palate and scrotum are not infrequent, while sloughing of the ears and external genitalia are common and characteristic lesions in the guinea pig. The tongue is generally covered with a heavy yellowish-white coat and the conjunctivæ are first congested, then frequently show a yellow tinge during the latter stages of the disease. The mind may be unusually clear to the last, or a low delirium may develop. Constipation and albuminuria are common and extreme lassitude is the rule. The temperature is continuous, moderately high, and lasts from one week to ten days in uncomplicated cases, but may be prolonged by septic complications. The pulse and respiration are rapid, the former out of proportion to the degree of temperature, showing the effect of the extreme toxemia. In cases progressing to recovery the temperature drops rapidly and convalescence is slow but complete.

Diagnosis.—The diagnosis of Rocky Mountain spotted fever should be made from the history of the case and character of the eruption. A correct diagnosis should easily be arrived at after the petechial eruption has appeared, except in those rare cases where the history does not exclude the possibility of *typhus fever infection*. In such cases blood inoculations into guinea pigs will establish the diagnosis, because these two diseases are easily distinguishable in this animal, both by the character of the lesions and by the absence of cross-immunization.

Rocky Mountain spotted fever is a rural rather than an urban disease, and the history of a case, if carefully investigated, will always show the probability of tick bite. Usually the patient has made a visit into tick-infested territory within the incubation period of the disease, from three to twelve days previous to the onset of sickness. The history of tick bite or possible exposure is thus commonly shown, or the tick may even be found attached in some obscure part of the body—scalp, axilla, navel or back. Occasionally no history of tick bite can be obtained, the tick having attached and dropped off without the patient's knowledge, and in such cases it is difficult to locate the bite. This feeding habit is not unusual with male ticks.

In the Idaho strain of Rocky Mountain spotted fever and the milder cases of the Bitter Root strain a slightly elevated, macular, roseolar eruption frequently makes its appearance on the face, neck, hands and upper thorax of the patient before the characteristic petechial eruption of the disease is visible. This early eruption may be easily mistaken for that of *measles* or early *small-pox*, and it is possible to confuse it with the eruptions seen in *other exanthematous febrile diseases*. It does not show, however, the crescentic arrangement of a measles eruption or the progression to vesicles and pustules seen in small-pox. This primary eruption in Rocky Mountain spotted fever should not be confused with

PLATE I.



Rocky Mountain Spotted Fever Showing Fully Developed Eruption

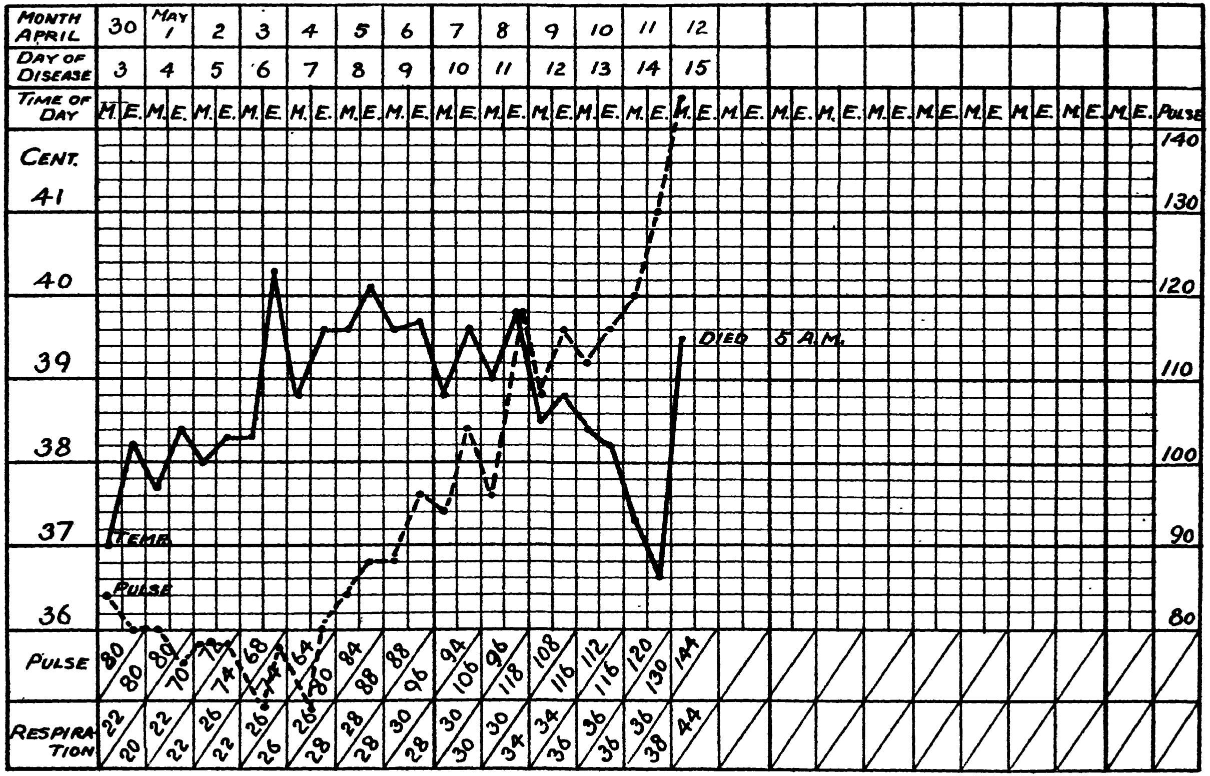


Fig. 1.—Typical Chart of Severe Human Case of Rocky Mountain Spotted Fever.

the early appearing erythema or diffused red blush of *scarlet fever,* with the rapidly changing crop-like papules and vesicles of *chickenpox,* with the localized abdominal rose spots of *typhoid fever,* nor with the infrequent and variable eruption of *epidemic cerebrospinal meningitis.*

Treatment.—Prophylaxis.—*Tick Eradication.*—Following the discovery that the wood tick (dermacentor) is responsible for the transmission of Rocky Mountain spotted fever to human beings, the Montana State Board of Health, the U. S. Public Health Service and the Bureau of Entomology have investigated different measures for tick eradication in the Bitter Root Valley of Montana, and while effective measures of tick control, adapted to any one locality, cannot be indiscriminately applied to another, the principles of tick eradication have without doubt been established.

These investigations have demonstrated that the abundance of dermacentor ticks in any locality is dependent upon their food supply, that is, suitable small animals to serve as hosts for the immature ticks and larger animals in proper abundance to serve as hosts for the adult ticks, while weather conditions and elevation play minor parts in tick infestation.

The following measures proposed for tick control have been carefully investigated in the Bitter Root Valley:

1. Clearing, fencing and cultivating arable lands.
2. Proper grazing laws.
3. Destruction of small, wild animals (rodents).
4. Dipping and spraying of horses and cattle.
5. Sheep grazing.
6. Burning over of foothills and "slashing."

1. Wherever large tracts of land are fenced and placed under close cultivation, ticks will be entirely eradicated within a few years, because they are thereby deprived of their food supply. Already this has been accomplished in many heavily tick-infested localities, and this method of tick eradication will continue without effort or interruption with the increase of intensive farming.

2. In many localities horses and cattle serve as the most common hosts of adult dermacentor ticks. In such places tick infestation can be reduced by proper grazing laws, which will keep these domestic animals off the open ranges during spring and early summer.

3. The destruction of small wild animals which serve as hosts for the immature ticks is a most important measure in tick eradication. This can be accomplished by poisoning, trapping and shooting. Poisoning with strychnin is the most effective method and should be conducted early in the spring and again in midsummer. Trapping should be continued by individual farmers throughout the season, and shooting with small caliber rifles may be employed to advantage under certain conditions. The farmers are apt to support a movement for the killing of

small rodents, because, in addition to serving as hosts for immature ticks, they are also serious agricultural pests.

4. Because of the success which had attended the dipping of cattle in arsenical dips, as a means of destroying the tick (*Margaropus annulatus* Say), vector of Texas cattle fever, it was unfortunately concluded that a similar dipping of horses and cattle would bring about the destruction of dermacentor ticks. This did not prove to be the case, because of differences in feeding habits of the two species of ticks, the short period of attachment of adult dermacentor ticks to their hosts, the attachment of immature ticks to entirely different hosts, and the difficulties attending the dipping of live stock in early spring in the Bitter Root Valley. For these reasons this method of tick eradication, after thorough investigation, has been abandoned in the Bitter Root Valley, Montana.

5. Investigations have shown that sheep lend themselves to being grazed in such a manner as greatly to reduce tick infestation. While grazing they pick up more adult ticks than do the larger domestic animals. Sheep graze closer and thus destroy the food and shelter of small rodents and ticks; they force the removal from the range of the larger animals, domestic and wild, and they destroy many ticks by means of the lanolin in their wool. By grazing sheep away from the settlements into the mountains each spring and returning them in autumn, they can be used in a mechanical way to sweep the infesting ticks back into remote places where they are not dangerous to the community. Thus sheep offer an opportunity to use waste lands in the vicinity of settlements for grazing purposes without increasing tick infestation.

6. The burning of undergrowth has not been found successful as a method of tick destruction. Unless repeated yearly it is apt to create rather than destroy a favorable tick environment, and at those times when weather conditions render it possible, burning is likely to spread beyond control and do great damage to the forests.

Prevention of Infection.—The safest way to prevent Rocky Mountain spotted fever infection is to **avoid visiting known infected areas during the tick season.** Where this is impossible a certain degree of protection is afforded by wearing **proper clothing,** but too great reliance should not be placed upon this uncertain defense. A feeling of false security in an infected tick country is dangerous. The wearing of high boots, the use of garments made with a minimum of openings and seams, with the upper garment well tucked inside and not outside of the lower, affords some protection against tick bites, as ticks ordinarily crawl up the body before attaching. In visiting heavily tick-infested territory the only protection against tick bites worth while is to **strip and search carefully for ticks** at from two to three-hour intervals. The search of one's clothing cannot be made with too great care. Infection may sometimes be prevented by promptly **cauterizing** a recent tick bite with a toothpick dipped in 95 per cent. carbolic acid.

General Measures.—Rocky Mountain spotted fever is a self-limited, specific, infectious disease and therefore, until specific therapy has been evolved against its causative organism and toxin, **symptomatic treatment** and **supportive measures** alone can be relied upon to assist the patient toward recovery. In this, as in all other specific diseases, many medicines have been acclaimed as certain cures, but on further trial they have been discarded for other equally ineffectual measures. **Wild sage tea** was the first treatment adopted, and maintained its popularity for many years, perhaps because of certain virtues it possessed as a diuretic and diaphoretic. This was followed by **quinin** and the **arsenical preparations,** both of which have been tried and generally abandoned.

The lack of a specific in the treatment of this disease, however, does not warrant an attitude of hopeless inactivity toward the patient. Without over-drugging, the careful practitioner will assist his patient to **eliminate the toxins** being produced in his body, will **support him during the period of invasion,** and will use every feasible measure for securing the **complete rest and comfort** which is necessary for the successful termination of a fight against this infection.

SERUM THERAPY.—Up to the present time no great progress has been made in the development of a specific treatment in Rocky Mountain spotted fever infection. Passive immunity to Rocky Mountain spotted fever virus may be established in susceptible animals by the injection of serum from an animal which has recovered from the disease, and susceptible animals may be protected from infection by the prompt injection of immune serum in proper dosage. Neither of these measures, however, is of practical utility in the protection of human beings against Rocky Mountain spotted fever infection. The serum obtained from man or other animals recovered from Rocky Mountain spotted fever infection has very little curative power, and therefore has not been found of great value in the treatment of the disease. Nor, according to Ricketts, is there a hope of obtaining a stronger serum for curative purposes until the specific organism of Rocky Mountain spotted fever has been cultivated.

Pathology.—The specific lesions of Rocky Mountain spotted fever in human beings and in experimental animals are characteristic of the disease and can be confused only with those of typhus fever. The lesions in man, monkeys and guinea pigs bear a striking resemblance and vary only in degree and selection of organs involved. The specific lesions are referable to the vascular system and manifest themselves in gross appearance by a moderate, general, glandular enlargement, marked enlargement of the spleen and hemorrhages into the deeper layers of the skin.

BLOOD-VESSELS.—The lesions of the blood-vessels begin with a proliferation of the endothelial cells, followed by thrombosis, occlusion and perivascular accumulations of large mononuclear cells. The alterations in the blood-vessels and the mechanical effects of these changes give rise to the edema, hemorrhagic rash, focal necroses and the necrotic areas frequently seen. They are also responsible for the sloughing of the ears, external genitalia and the skin over the dependent parts of the body.

Lymph-Glands.—The sinuses are distended with large mononuclear, phagocytic cells. Congestion is marked and hemorrhages are frequently noted in all infected animals.

Spleen.—There is intense engorgement and enlargement of the spleen to two or three times its normal size with accumulation of great numbers of large mononuclear phagocytic cells in the sinuses and reticular tissue. The enlargement of the spleen, while pronounced in man, monkeys and guinea pigs, is enormous in white rats.

Skin.—The lesions of the blood-vessels in the deeper layers of the skin are characteristic of Rocky Mountain spotted fever. These lesions consist of an endothelial cell proliferation, thrombosis, occlusion and perivascular accumulation of large mononuclear cells. Skin lesions are striking in man, less so in monkeys and least noticeable in guinea pigs and rats.

There is evidence of the production of an endothelial toxin in the increase of large mononuclear cells of the blood and their accumulation in the lymph-glands and spleen of infected animals.

Historical Summary.—No records were kept by the Indians of any of the events which transpired in the Rocky Mountain region previous to the coming of white men, and therefore, no history of Rocky Mountain spotted fever should be expected to antedate their advent.

Early settlers, however, have reported that a tradition existed among the Shoshone Indians of the Wind River Mountains and also among the Black Foot Indians of the Bitter Root Valley, to the effect that no one could visit sections of these mountains at certain seasons of the year without making the Great Spirit angry. It is possible, though by no means certain, that this superstition was based upon the presence of spotted fever infection in these mountains.

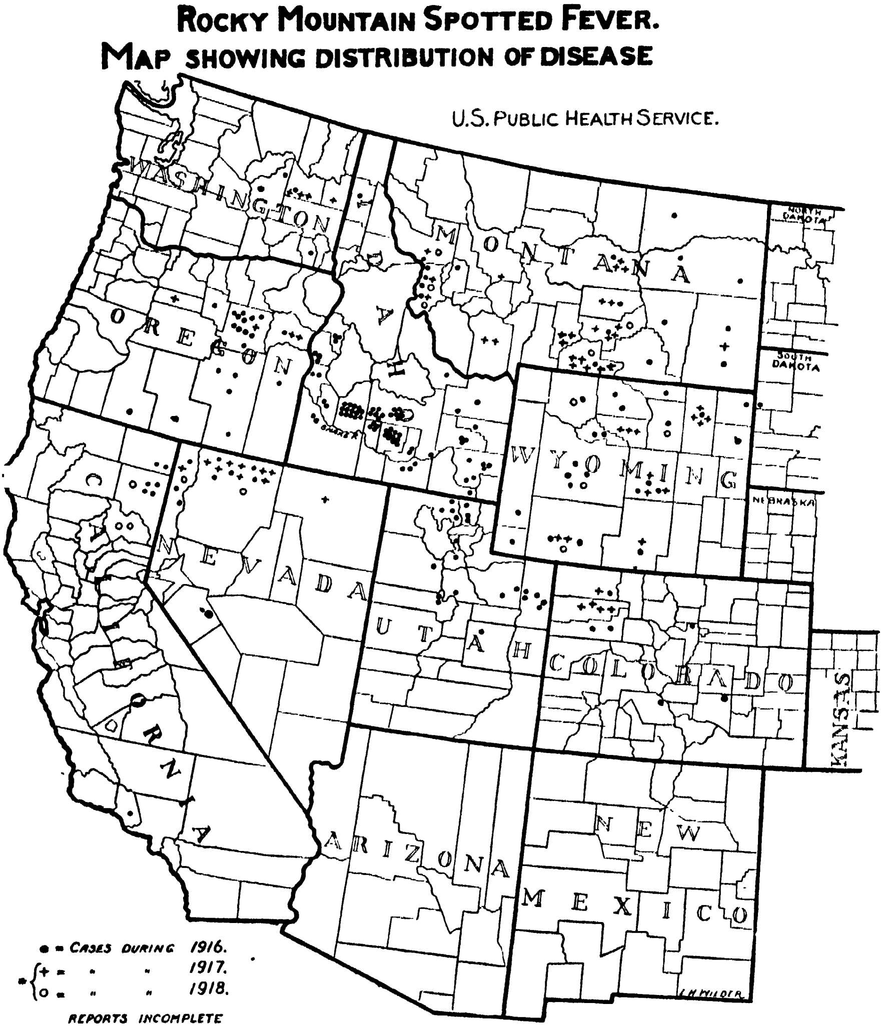
The comprehensive report of the Lewis and Clark expedition which, in 1805-1806, traversed the northern part of the territory now known to contain ticks infected with Rocky Mountain spotted fever virus, neither mentions the presence of these ticks nor the occurrence of a disease among the party, which might have been Rocky Mountain spotted fever; although the report does make bitter complaint of the mosquitoes frequently encountered, and also records the presence of trachoma among the Columbia River Indians and the calamity of blindness which had resulted from this disease.

The observations and records made by early explorers and trappers who followed the Lewis and Clark expedition to the head waters of the Missouri and Columbia rivers amount to little more than those of the Indians themselves and, therefore, it is hardly to be wondered at that no evidence bearing upon the presence or absence of the disease comes from them. It was not until the Mormon immigration into Utah, in 1847, and the great transcontinental movement to the California gold fields a few years later, that definite rumors—though with vague case histories—indicate the first encounter of white men with Rocky Mountain spotted fever. These rumors of "bull fever," "mountain fever," "typho-malaria fever of the Rocky Mountains," "black fever," "blue disease," and "spotted fever," occurring along the Overland Trail in southwestern Wyoming and the Great Basin Country of northern Utah and southern Idaho, undoubtedly included some cases of Rocky Mountain spotted fever. During the next fifty years the majority of these early observers, including U. S. Army Surgeons stationed at Army posts in the Rocky Mountain region, confused Rocky Mountain spotted fever with other well-known diseases of the East, with which they were familiar, claiming that these diseases had been altered by climate and altitude, so as to present the clinical picture seen in Rocky Mountain spotted fever. But since Rocky Mountain spotted fever is now known to be a distinct entity, it is inconceivable to think of the virus of this disease as having originated within very recent times. It is therefore practically certain that it has existed among the ticks and susceptible animals of the Rocky Mountain region for centuries at least.

In 1899, Dr. E. E. Maxey, of Boise, Idaho, carefully described Rocky Mountain spotted fever clinically, and clearly differentiated it as a new and specific disease, which classification was generally accepted by the medical profession within the next few years.

Geographical Distribution.—Rocky Mountain spotted fever is a disease of the Rocky Mountain region of the United States that has recently spread to the Pacific Coast in Southern California. So far as known, it has never been contracted elsewhere, and no other disease resembles it closely in clinical appearance except typhus fever and, possibly, tsutsugamushi disease of Japan.

Since its recognition, Rocky Mountain spotted fever is known to have recurred from year to year, with little variation in locality, within certain endemic areas scattered through the nine Rocky Mountain states, as follows: Montana, south-central and southwestern parts of the state, particularly Carbon, Missoula and Ravalli counties; Wyoming, scattered over the entire state except the southeastern portion (Platt, Goshen and Larimie counties), most abundant in Natrona County, the Wind River Reservation in Fremont County and along the Big Horn River and its tributaries; Colorado, a very few widely scattered foci of infection extending from Denver throughout the northwestern part of the state, cases having been reported from the vicinity of Carbondale, Glenwood Springs and Rifle in Garfield County, and from Routt, Meeker and Moffatt counties; Idaho, numerous endemic areas in the Snake River Valley and along its northern tributaries the Boise, Payette, Wood and Weiser Rivers, also in Bannock County in the southeastern part of the state and scattered foci in the northern part of the state; Utah, most abundant in the northern part of the state in Box Elder, Cashe, Utah and Wasatch counties, but scattered cases reported as far south as the central part of the state; Nevada, reports of endemic areas in Washoe, Humboldt and Elko counties, particularly from Quinn River Valley and Paradise Valley in the northern part of the state, also scattered foci as far south as Mineral County in the extreme western part of the state; Washington, endemic foci in the coulées of the Big Bend Country of the Columbia River west of Spokane in Douglas, Grant, Lincoln and Adams counties; Oregon, areas of infection east of the Cascade Mountains in Jefferson,



G. 2.—Distribution of Rocky Mountain Spotted Fever in the United States.

Crook, Lake, Klamath, Grant, Harney and Malheur counties; California, long established areas of infection in Modoc and Lassen counties in the extreme northeastern part of the state. These endemic areas of infection have been definitely determined by reports of human cases recurring therein from year to year, while from other tick-infested localities of the Rocky Mountain region where many persons have been tick bitten yearly, no case of Rocky Mountain spotted fever has ever developed. It is obvious, therefore, that the total infected area, as compared with the 600,000 square miles of tick-infested territory within the Rocky Mountain region, is small, and the delineation of infected from non-infected territory is frequently sharp and has persisted over years of unrestricted inter-communication.

In addition to these well-known areas of infection, the first wide extension of the disease in recent years occurred in 1915, involving southeastern Montana, particularly Rosebud, Custer and Fallon counties and Butte County, South Dakota, which marks the eastern limit of the disease up to the present time. In 1916, one case was infected in Ventura County, California, this being the first case reported west of the Coast Range Mountains, and also marking the southern limit of the disease as reported up to the present time.

In evaluating these reports of Rocky Mountain spotted fever occurrence among human beings, however, it should be borne in mind that this entire region is sparsely settled; that the settlements have been most numerous along the water courses, where the endemic areas of infection are most commonly located; that many persons who are infected outside of these settlements are never seen by a physician; and that infected ticks and animals will remain undetected in any locality until a human being visits it, is bitten and develops the disease.

Because of the complicated relationship which exists between the virus of Rocky Mountain spotted fever, the ticks which transmit the disease, and the animal hosts of these ticks, it would be extremely difficult for Rocky Mountain spotted fever to establish itself and spread anywhere east of the Rocky Mountain foothills under farming conditions as they exist in the eastern states.

BIBLIOGRAPHY

Anderson, J. F. Spotted fever (tick fever) of the Rocky Mountains, a new disease. Am. Med., Philadelphia, vi, 506-508. Bull. No. 14, U. S. Pub. Health and Mar.-Hosp. Serv., Hyg. Lab., 1903, Govt. Print. Office.

Anderson, J. F., and Goldberger, J. On the relation of Rocky Mountain spotted fever to the typhus of Mexico. Pub. Health Rep., U. S. Pub. Health and Mar.-Hosp. Serv., Wash., 1909, xxiv, 1861.

Anderson, R. Historical, laboratory, and clinical observations in so-called Rocky Mountain spotted fever. Utah Med. Jour. (Denver Med. Times), 1908-9, xxvii, 516-522

Ashburn, P. M. Piroplasma hominis (?)-spotted fever in Montana. Lancet-Clinic, Cincinnati, 1905, n. s. liv, 494-505.

——— A suggestion as to the treatment of spotted fever of Montana. *Ibid.*, 579-584.

Ashburn, P. M., and Craig, C. F. A comparative study of tsutsugamushi disease and spotted or tick fever of Montana. Philippine Jour. Sc., 1908, Sec. B, iii, 1-29; Boston Med. and Surg. Jour., 1908, clviii, 749-761.

Banks, N. The scientific name of the spotted-fever tick. Jour. Am. Med. Assn., Chicago, 1910, lv, 1574-1575.

Birdseye, C. *See* Henshaw, H. W.

Bishop, F. C. The distribution of the Rocky Mountain spotted-fever tick. U. S. Dept. Agric., Bur. of Entomology, Circ. No. 136, Wash. Govt. Print. Office, 1911. (*See also* Hunter, W. D.)

Bishop, F. C., and King, W. V. Additional notes on the biology of the Rocky Mountain spotted-fever tick. Jour. Econom. Entomol., Concord, N. H., 1913, vi, 200-211.

Boggs, Thomas R. In Osler's Modern medicine, 1907, Vol. III, 535, Lea and Febiger, Philadelphia.

Broden, J. M. Some observations on four cases of spotted fever occurring in Colorado. Colorado Med., Denver, 1906, iii, 213-219.

Castellani, A., and Chalmers, A. J. Spotted fever of the Rocky Mountains. Manual of Trop. Med., Wm. Wood & Co., N. Y., 1910, pp. 712-717.

Chowning, W. M. Studies in Rocky Mountain spotted fever. Jour. Minnesota Med. Assn., Minneapolis, 1908, xxvii, 45-49. (*See also* Wilson, L. B.)

——— Rocky Mountain spotted fever. Preliminary reports. *Ibid.*, 1907, xxvii, 101.

Studies in Rocky Mountain spotted fever. *Ibid.*, 1908, xxviii, 45-49.

Christy, C. Ornithodorus Moubata and tick fever in man. Brit. Med. Jour., London, 1903, ii, 652-653.

Cobb, J. O. The so-called "spotted fever" of the Rocky Mountains. A new disease in the Bitter Root Valley, Montana. Pub. *Health* Rep., U. S. Pub. Health and Mar.-Hosp. Serv., Wash., 1902, xvii, *1866-1870*.

Cooley, R. A. Preliminary *report on the wood tick.* Bull. 75, Montana Experiment *Station, Bozeman, Mont., 1908.*

——— Tick control in relation to the Rocky *Mountain spotted* fever. *Ibid.*, Bull. 85, 1911.

——— Notes on little known habits of the Rocky Mountain spotted-fever tick (*Dermacentor venustus,* Banks). Reprint. Jour. Economic Entomol., 1913, vi, No. 1.

——— The spotted-fever tick (*Dermacentor venustus,* Banks) and its control in the Bitter Root Valley, Mont. A Review. Reprint. *Ibid.,* 1915, viii, No. 1.

Craig, C. F. The relation of the so-called Piroplasma hominis and certain degenerative changes in the erythrocytes. Am. Med., Philadelphia, 1904, viii, 1016-1017.

Cummings, Jas. G. Rocky Mountain spotted fever in California. Reprinted from the Jour. of Infect. Dis., Nov., 1917, xxi, No. 5, 509-514.

Davis, B. F. Unfinished experiments of Dr. Howard T. Ricketts on Rocky Mountain spotted fever. Contrib. to Med. Science, Univ. of Chicago Press, Chicago, 1911, 409-418.

Davis, B. F., and Peterson, W. F. Complement deviation in Rocky Mountain spotted fever. Jour. Infec. Dis., 1911, viii, 330-338. *See also* Contrib. to Med. Science, Ricketts, Univ. of Chicago Press, 1911, 419-427.

Fricks, L. D. Rocky Mountain spotted fever. Sheep grazing as a possible means of controlling the wood tick (*Dermacentor andersoni*) in the Bitter Root Valley. Reprint. from Pub. Health Rep., Aug. 8, 1913.

——— Rocky Mountain spotted fever. A report of its investigations and of work in tick eradication for its control during 1913. Reprint. from Pub. Health Rep., Feb. 20, 1914.

Rocky Mountain spotted fever. Some investigations made during 1912 by P. A. Surgeon, T. B. McClintic. Prepared for publication by L. D. Fricks. Reprint. from Pub. Health Rep., Apr. 24, 1914.

Fricks, L. D. Rocky Mountain spotted fever. A report of its investigations, and of measures undertaken for its eradication during 1914. Reprint. from Pub. Health Rep., Jan. 15, 1915.

——— Rocky Mountain spotted fever. A report of laboratory investigations of the virus. Reprint. No. 327 from Pub. Health Rep., Mar. 3, 1916.

——— Rocky Mountain spotted fever. Some points in its diagnosis and prevention. Supplement No. 28, Pub. Health Rep., Mar. 17, 1916.

Geary, J. W. A case of spotted fever. Med. Sentinel, Portland, Oregon, 1905, xiv, 32.

Goldberger, J. *See* **Anderson, J. F.**

Gomez, L. Rocky Mountain spotted fever in the rabbit. Jour. Infect. Dis., Chicago, 1909, vi, 382-386. (*See also* **Ricketts, H. T.**)

Gwinn, R. The so-called spotted fever. Missoulian, Missoula, Mont., 1902.

Hazlett, H. W. Rocky Mountain fever; tick fever; blue disease. Colorado Med., Denver, 1912, ix, 185-87.

Heinemann, R. G., and Moore, J. J. The production and concentration of a serum for Rocky Mountain spotted fever. Jour. Am. Med. Assn., Chicago, 1911, lvii, 198.

——— Experimental therapy of Rocky Mountain spotted fever; the preventive and curative action of a serum for spotted fever, and the inefficiency of sodium cacodylate as a curative agent for this disease in guinea pigs. Jour. Infect. Dis., Chicago, 1912, x, 294-304.

Henshaw, H. W., and Birdseye, C. The mammals of the Bitter Root Valley, Montana, in their relation to spotted fever. U. S. Dept. Agric., Bur. Biolog. Surv., Circ. No. 82, Wash., Govt. Print. Office, 1911.

Higgs, deW. P. Rocky Mountain fever. Chicago Med. Times, 1908, xli, 272-274.

Hunter, W. D., and Bishop, F. C. Some of the more important ticks of the United States. Yearbook, U. S. Dept. Agric. for 1910, Wash., Govt. Print. Office, 1911.

——— The Rocky Mountain spotted fever tick. U. S. Dept. Agric., Bur. Entomol., Bull. 105, Govt. Print. Office, 1911.

Kelly, Frank I. Rocky Mountain spotted fever: its prevalence and distribution in Modoc and Lassen counties, California. Rep. Calif. State Jour. Med., Oct., 1916.

Kieffer, C. F. Intermittent tick fever. Preliminary report on a new type of fever due to tick bite (ixodiasis). Jour. Am. Med. Assn., Chicago, 1907, xlviii, 1154-1158.

King, W. W. Experimental transmission of Rocky Mountain spotted fever by means of the tick. Preliminary note. Pub. Health Rep., Wash., Govt. Print. Office, 1906, xxi, 863-864.

Kitashima, T., and Miyajima. Japanese river fever (tsutsugamushi). Kitasato Arch. Exper. Med., Tokyo, Dec., 1918, ii, No. 3, 237.

Le Count, E. R. A contribution to the pathological anatomy of Rocky Mountain spotted fever. Jour. Infec. Dis., Chicago, 1911, viii, 421-426. *See also* Contributions to Med. Science, Ricketts, Univ. Chicago Press, 1911, 445-450.

Manson, P. Spotted fever of the Rocky Mountains. Trop. Dis. Bull., London, 1903, xii, 174-176.

Marsden, W. L. Spotted fever in Oregon. Med. Sentinel, Portland, Oregon, 1903, xi, 389.

Maver, M. B. Transmission of spotted fever by the tick in nature. Jour. Infect. Dis., Chicago, 1911, viii, 322-324. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 437-439.

——— Transmission of spotted fever by other than Montana and Idaho ticks. *Ibid.*, 1911, viii, 327-331. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 440-444.

Maxey, E. E. Some observations on the so-called spotted fever of Idaho. Med. Sentinel, Portland, Oreg., 1899, vii, 433-438.

Maxey, E. E. Rocky Mountain spotted (tick) fever, with special reference to causal factors, mortality, and geographical distribution in Idaho. *Ibid.*, 1908, xvi, 666-678.

Mayo, H. N. Rocky Mountain or spotted fever. *Ibid., 1906,* xiv, 370.

——— Rocky Mountain spotted fever. Jour. Am. Med. Assn., *Chicago*, 1906, xlvii, 36.

Spotted fever. Denver Med. Times (etc.), 1906-7, xxvi, 67-69.

McCalla, L. P. Direct transmission from man to man of Rocky Mountain spotted fever. Med. Sentinel, Portland, Oreg., 1908, xvi, 187.

McClintic, T. B. Investigations of and tick eradication in Rocky Mountain spotted fever. Pub. Health Rep., U. S. Pub. Health and Mar.-Hosp. Serv., Wash., Govt. Print. Office, 1912, xxvii, 732-760. *See also* reprint from Pub. Health Rep. No. 79.

McCullough, G. T. Spotted fever. Med. Sentinel, Portland, Oreg., 1902, x, 225-228.

Milne, A. D. *See* Ross.

Montana State Board of Entomology. First Biennial Report, 1913-14; Second Biennial Report, 1915-16; Third Biennial Report, 1917-18.

——— Tick Control Program for 1919. March, 1919.

Montana State Board of Health. First Biennial Report, 1901-02; Second Biennial Report, 1903-04; Third Biennial Report, 1905-06; Fourth Biennial Report, 1907-08; Fifth Biennial Report, 1909-10; Sixth Biennial Report, 1911-12; Seventh Biennial Report, 1913-14; Eighth Biennial Report, 1915-16.

Moore, J. J. Time relationships of the wood tick in the transmission of Rocky Mountain spotted fever. Jour. Infect. Dis., 1911, viii, 339-350. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 428-436.

Mooser, C. E. Rocky Mountain spotted fever. Jour. Am. Med. Assn., Chicago, 1906, xlvii, 686.

Parker, R. R. Some results of two years' investigations of Rocky Mountain spotted fever tick in eastern Montana. Reprinted from the Jour. Economic Entomol., ii, No. 2, 1918.

Pearce, R. A. Tick or Rocky Mountain spotted fever. Utah Med. Jour. (Denver Med. Times), 1908-9, xxviii, 415.

Peterson, W. F. *See* Davis.

Ricketts, H. T. Contributions to Medical Science. Dedicated to H. T. Ricketts. Univ. of Chicago Press, 1911. Contains a summary of Rocky Mountain spotted fever work done by him.

The study of Rocky Mountain spotted fever by means of animal inoculations. Jour. Am. Med. Assn., Chicago, 1906, xlvii, 33-36; and *also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 278-287.

——— The transmission of Rocky Mountain spotted fever by the bite of the wood tick. *Ibid.*, 1906, xlvii, 358. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 287-290.

Further observations on Rocky Mountain spotted fever and Dermacentor occidentalis. *Ibid.*, 1906, xlvii, 1067-1069. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 291-298.

The rôle of the wood tick (*Dermacentor occidentalis*) in Rocky Mountain spotted fever, and the susceptibility of local animals to the disease. *Ibid.*, 1907, xlix, 24-27. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 312-323.

——— Further experiments with the wood tick in relation to Rocky Mountain spotted fever. *Ibid.*, 1907, xlix, 1278-1281. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 324-342.

——— Observations on the virus and means of transmission of Rocky Mountain spotted fever. Jour. Infec. Dis., Chicago, 1907, iv, 141-153. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 229-311.

Ricketts, H. T. Demonstrations of a microörganism which apparently has a specific relationship to Rocky Mountain spotted fever. Tr. Chicago Path. Soc., 1907-08, vii, 254.

——— A summary of investigations of the nature and means of transmission of Rocky Mountain spotted fever. *Ibid.*, 1907-08, vii, 73-82. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 333-342.

Recent studies of the Rocky Mountain spotted fever in Montana and Idaho. Med. Sentinel, Portland, Oregon, 1908, xvi, 668-697. (Discussion 704-711.)

General report of an investigation of Rocky Mountain spotted fever, carried on during 1906 and 1907. Fourth Bien. Report, State Board of Health of Montana, Helena, 1908, 86-130.

——— A report of investigations carried on during the winter of 1907-1908, and the spring and summer of 1908. *Ibid.*, 131-191.

Some aspects of the Rocky Mountain spotted fever as shown by recent investigations. (Carpenter lecture.) Med. Rec., New York, 1909, lxxvi, 843-855. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 373-408. *See also* Med. Sentinel, Portland, Oregon, 1909, xvii, 674-700.

A microörganism which apparently has a specific relationship to Rocky Mountain spotted fever. Jour. Am. Med. Assn., Chicago, 1909, lii, 379-384. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 368-372.

Investigations concerning Rocky Mountain spotted fever. Johns Hopkins Hosp. Bull., Baltimore, 1909, xx, 151.

Ricketts, H. T., and Gomez, L. Studies on immunity in Rocky Mountain spotted fever. Jour. Infec. Dis., Chicago, 1908, v, 221-244. *See also* Contrib. to Med. Science, Ricketts, Univ. Chicago Press, 1911, 343-367. (Abstracted in Science, New York and Lancaster, Pa., 1908, n. s., xxvii, 651.)

Ricketts, H. T., and Wilder, R. M. The relation of typhus fever (tabardillo) to Rocky Mountain spotted fever. Arch. Int. Med., Chicago, 1910, v, 361-370. *See also* Contrib. to Med. Science, Ricketts, 1911, Univ. Chicago Press, 479-490.

Robinson, A. A. Rocky Mountain spotted fever with report of a case. Med. Rec., New York, 1908, lxxiv, 913-922.

——— Rocky Mountain spotted fever. Jour. Trop. Med., 1910, xiii, 134-157-165.

Rosenau, M. J. Spotted fever. Practical treatment. Musser & Kelly, Philadelphia and London, 1911, ii, pp. 715-717.

——— Spotted fever. Textbook on Preventive Medicine and Hygiene.

Ross, P. H., and Milne, A. D. Tick fever. Brit. Med. Jour., London, Nov. 26, 1904, ii, 1453.

Rucker, W. C. The problem of Rocky Mountain spotted fever. The Military Surg., Wash., 1911, xxix, No. 6, 631-657.

——— Rocky Mountain spotted fever. Sept. 6, 1912. Reprint from Pub. Health Reports.

Sambon, L. W. The spotted fever of the Rocky Mountains. In Albutt and Rolleston's System of medicine, 1907, ii, pt. 2, 307-313.

Smith, R. J. A case of spotted or tick fever. Alkaloid. Clin., Chicago, 1904, xi, 1252-1254.

Smith, W. F. *See* Stewart.

Spencer, W. O. Mountain or spotted fever, as seen in Idaho and eastern Oregon. Med. Sentinel, Portland, Oregon, 1907, xv, 532-537.

Stewart, J. L., and Smith, W. F. Clinical phases of Rocky Mountain spotted fever. *Ibid.*, 1908, xvi, 704-711.

Stiles, C. W. A zoölogical investigation into the cause, transmission and source of the so-called Rocky Mountain spotted fever. Pub. Health Rep., 1904, xix, 362-1649.

STILES, C. W. Preliminary report upon a zoölogical investigation of the so-called spotted fever of the Rocky Mountains. Ann. Rep., Surg. Genl., U. S. P. H. and Mar.-Hosp. Serv., 1904, Wash., Govt. Print. Office, 1904, 362-363.

——— Preliminary report upon a zoölogical investigation into the cause, transmission and source of the so-called spotted fever of the Rocky Mountains. Pub. Health Rep., U. S. Pub. Health and Mar.-Hosp. Serv., Wash., 1904, xix, 1649.

A zoölogical investigation into the cause, transmission and source of Rocky Mountain spotted fever. Bull. 20, U. S. Pub. Health and Mar.-Hosp. Serv., Hyg. Lab., Wash., Govt. Print. Office, 1905.

Zoölogical pitfalls for the pathologist. Proc. New York Path. Soc., 1905, 1-21.

——— The common tick (*Dermacentor andersoni*) of the Bitter Root Valley. Pub. Health Rep., U. S. Pub. Health and Mar.-Hosp. Serv., Wash., Govt. Print. Office, 1908, xxiii, 949.

The taxonomic value of the microscopic structure of the stigmal plates in the tick genus Dermacentor. Bull. 62, U. S. Pub. Health and Mar.-Hosp. Serv., Hyg. Lab., Wash., Govt. Print. Office, 1910.

The correct name of the Rocky Mountain spotted-fever tick. Jour. Am. Med. Assn., Chicago, 1910, lv, 1909-1910.

STITH, R. M. Tick fever, with report of a case. Northwestern Med., Seattle, 1905, iii, 201-205.

STOTES, G. W. Tick fever, or Rocky Mountain spotted fever. Utah Med. Jour. (Denver Med. Times), 1908-09, xxviii, 522-526.

TUTTLE, T. D. Some indications for State control of Rocky Mountain tick fever. Med. Sentinel, Portland, Oregon, 1908, xvi, 697-711.

WILDER, R. M. *See* RICKETTS.

WILSON, L. B., AND CHOWING, W. M. The so-called "spotted fever" of the Rocky Mountains. A preliminary report to the Montana State Board of Health. Jour. Am. Med. Assn., Chicago, 1902, xxxix, 131-136.

——— The hematozoön of the so-called spotted fever of the Rocky Mountains. Northwest Lancet, Minneapolis, 1902, xxii, 440-442.

——— Spotted fever of Montana. Med. Sentinel, Portland, Oregon, 1902, x, 238-239.

——— Report on the investigation of so-called spotted fever. First Bien. Rep., Montana State Board of Health, 1903, 26-91.

Studies in pyroplasmosis hominis, "spotted fever" of the Rocky Mountains. Jour. Infect. Dis., Chicago, 1904, i, 31-57.

WOLBACH, S. B. The demonstration of a parasite in the lesions of experimental Rocky Mountain spotted fever in monkeys and guinea pigs. Jour. Med. Research, xxxiv, No. 1, March, 1916.

——— The etiology of Rocky Mountain spotted fever. Jour. Med. Research, Sept., 1916, xxxv, No. 1, pp. 147-150.

The etiology and pathology of Rocky Mountain spotted fever. *Ibid.*, xxxvii, No. 3, pp. 499-508, Jan., 1918.

WOOD, M. W. Spotted fever as reported from Idaho. Rep. Surg. Genl., U. S. Army, 1896, Wash., Govt. Print. Office, 1896, 60-65.

CHAPTER XLIV

GLANDERS

By Henry Wolfer, M.D.

Synonyms, p. 69—Definition, p. 69—Etiology, p. 69:—Predisposing causes, p. 69; Exciting cause: the organism, p. 69:—General characteristics, p. 69; *Cultivation*, p. 70; Distribution, p. 71; Modes of conveyance, p. 71—Symptomatology, p. 72:—Acute glanders, p. 72; Chronic glanders, p. 73; Laboratory findings, p. 74—Diagnosis, p. 74—Treatment, p. 75:—Prophylaxis, p. 75; General management, p. 75; Medicinal treatment, p. 76; Specific therapy, p. 76; Surgical treatment, p. 76—Prognosis, p. 76—Pathology, p. 76—Historical summary and distribution, p. 77.

Synonyms.—*Farcy;* French, *morve, farcin;* German, *Rotzkrankheit, Wurmkrankheit;* Spanish, *muermo;* Italian, *morva* (*farcino*); Latin, *malleus, equinia.*

Definition.—Glanders is a specific infectious and contagious disease of the genus Equus (horse, mule, ass), caused by the *Bacillus mallei* and occasionally transmitted to man, usually by accidental inoculation of the skin or through the nasal mucous membrane. It is readily transmitted to certain animals, as the cat, dog and guinea pig, and with difficulty to sheep and goats. Cattle seem to be immune. In man the disease may run an acute or chronic course. The term *glanders* is sometimes limited to that condition in which the glanderous lesions are situated in the nasal mucous membrane and internal organs, and the term *farcy* is employed when the lesions appear in the skin and lymphatics.

Etiology.—Predisposing Causes.—The principal predisposing factor depends upon occupations in which intimate and direct contact with glandered horses is apt to occur. Thus the disease is most frequently observed in men, during the active period of life, who are occupied as farmers, stablemen, coachmen, tanners, veterinarians, etc. Bacteriologists working with the bacillus and those performing autopsies on glandered bodies have been accidentally infected. Those in attendance on human cases of the disease or who handle objects soiled with the discharges and secretions may become infected. The disease is rarely transmitted to women, as the principal predisposing factor is lacking.

Exciting Cause: The Organism.—*General Characteristics.*—The causative agent is the *Bacillus mallei.* It is a short, rod-like organism resembling the tubercle bacillus, and is from 3 to 4 microns long and from 0.25 to 0.50 micron wide. It shows rounded ends, and at times presents a slightly curved form and after staining, a beaded appearance similar to the Klebs-Loeffler bacillus. It is aërobic non-spore-bearing, and is said by most observers to be non-motile. The bacillus stains readily with the ordinary basic aniline dyes, and is negative to Gram's method. In tissue sections it is difficult to demonstrate its presence, on account of the cell detritus present and the ease with which it releases the stain. Thionin blue or carbol gentian violet may be used for tissue staining. It may then be decolorized for five to ten seconds with a 4 per cent. solution of acetic acid.

Cultivation.—The bacillus grows fairly well on the ordinary culture media, best at a temperature of 33° to 37° C. (91.4° to 98.6° F.), and when the media is slightly acid. Acid glycerin agar and potato are usually employed for direct cultural purposes. On the former a greyish-white transparent growth appears in twenty-four hours. On the potato the growth is extremely characteristic and of great diagnostic value. It appears in forty-eight hours as a honey-like or brownish deposit, which spreads and covers the surface by the end of a week. During this time it assumes the typical chocolate-colored growth with bluish-green margins. The *Bacillus pyocyaneus* may give a somewhat similarly colored growth on the potato. Bouillon is uniformly clouded with the formation, after a few days, of a stringy, slimy deposit. Successive generations of the *Bacillus mallei* grown on artificial media rapidly lose their virulence, although some strains have been known to retain it for months. The virulence from various equine cases of glanders often shows marked variation. It is greatly enhanced by transmission through man, and for this reason infection from human cases is apt to produce an acute and rapidly fatal type of the disease.

The bacillus, when unprotected by foreign materials such as the discharges, dirt, etc., is not a very resistant type of bacteria to chemical or physical changes. Exposure to the sun's rays destroys it in twenty-four hours, and it loses its virulence after drying within ten to fifteen days. In a moist condition the bacilli may remain alive for months, and are said to resist putrefactive changes for a period of thirty days. In the common watering trough they may remain alive for seventy days.

Cultures are destroyed by heating to 70° C. (158° F.) for one hour. A solution of corrosive sublimate 1:1000 destroys the bacilli in fifteen minutes, a 5 per cent. solution of phenol in thirty minutes. They are very sensitive to solutions of hypochlorite.

Mallein is the watery, glycerin extract of the virulent *Bacilli mallei*, and contains the specific toxin. It is obtained by methods similar to that advocated by Roux. The organism is cultivated in a 5 per cent. glycerin broth for six weeks, is then boiled and concentrated to one-half its original volume. This is filtered through a Berkefeld candle filter, and the filtrate diluted with an equal volume of a 1 per cent. solution of phenol. Mallein is employed for the diagnosis of glanders in the horse. Typical reactions follow its intracutaneous or subcutaneous injection and also after instillation in the conjunctival sac of infected animals.

It is often extremely difficult to obtain the bacilli direct from the suspected material, and thereby establish a positive diagnosis. A direct culture on the potato or acid glycerin agar may be made and the growth examined microscopically, and an aqueous suspension of the suspected material injected into the peritoneal cavity or abdominal wall of an adult male guinea pig. This animal inoculation is called the Strauss test or reaction, and produces typical findings if the material contains the bacilli. After a variable period of time—usually within one week—the testicle of the animal becomes swollen and inflamed, and the organism can be obtained from between the layers of the tunica vaginalis. In many cases the typical reaction does not follow the injection of the suspected material and, in addition, an aqueous suspension of the potato growth is injected into another guinea pig.

Distribution.—(*a*) *In the Body.*—The bacilli are found in all glanderous lesions and their discharges throughout the body, and, depending on the area involved, the conjunctival, nasal and bronchial secretions may be infected. The lymph-glands in proximity to the primary focus of infection are early infected. The discharges from chronic lesions are apt to contain fewer virulent bacilli. They are frequently found in the saliva and occasionally in the urine and circulating blood. Positive blood cultures are found in those cases showing acute manifestations and usually three or four days before a fatal termination. The stools may contain the bacilli when lesions are present in the intestinal mucosa or by ingestion from lesions in the nasopharynx.

(*b*) *Outside of the Body.*—The distribution of the bacilli outside of the body is confined in great part to such objects readily contaminated by the discharges, secretions, or excretions, from animal or human cases of the disease. In a stable the harness, blankets, curry-combs, etc., often transmit the disease to healthy animals, and the feed boxes and watering trough are also important means for its dissemination. The dust about a stall, in which a glandered horse has been stabled, may contain the organism. From human cases of the disease the bacilli are transmitted by the discharges, soiled dressings, clothes, drinking vessels, etc.

Modes of Conveyance.—(*a*) *Contagion.*—Transmission of the disease to man takes place by direct contact with equine or human cases of the disease or, indirectly, from various objects contaminated with material containing the *Bacilli mallei.*

(*b*) *Inoculation.*—In man the bacilli gain entrance through the skin or mucous membranes, the former being the most common mode. It is held that infection through the intact skin does not occur, a wound or the slightest abrasion being necessary before the bacilli can pass through. The various mucous membranes are readily infected; that of the vagina may be primarily involved by coitus.

(*c*) *Infection by Ingestion.*—Infection through the alimentary tract is believed by some to be more frequent than is generally realized at the present time. The early diarrhea and other symptoms observed in some cases before any localizing foci appear apparently indicate a primary intestinal involvement. M'Fadyean and others maintain gastro-intestinal infection to be common in the horse. Feeding menagerie animals, such as lions, wolves, etc., with the meat of a glandered horse results in the production of the disease.

(*d*) *Infection by Inhalation.*—Infection through the lungs by inhalation of the bacilli has been demonstrated as a possibility by laboratory experiments. A case has been described in the literature, in which infection undoubtedly took place in this manner. However, so far as it concerns human infections, it appears to be of minor importance.

Symptomatology.—ACUTE GLANDERS.—The period of incubation is usually from two to five days, though it has been reported to have lasted from two to three weeks. Cases developing weeks or months after the definite time of exposure are probably latent types of the infection. The disease begins with a local inflammatory reaction at the site of inoculation, and this is usually located on the upper or lower extremity, face or neck. The inflammation is phlegmonous or erysipelatous in type and shows an early tendency to break down and form an ulcer. Lymphangitis and lymphadenitis soon appear, and in the inflammatory zone surrounding the ulcer we find the formation of vesicles, pustules, and at times gangrenous areas develop. Subcutaneous, cutaneous, and muscular foci of glanderous nodes and nodules make their appearance usually during the second week, and these constitute the most characteristic and constant feature of the disease. They are most commonly seen on the lower extremities, regardless of the location of the primary site of infection. These solid or softening growths may be extremely painful and show an inflammatory reaction. Rapid necrosis sets in, with the formation of abscesses, ulcers, and deep sinuses, discharging a characteristic yellowish, oily material. At times this process is so extensive that the underlying muscles, fascia, and even bones may be exposed. An eruption, either localized usually to the face and neck, or general in its distribution, then develops. It appears in crops, first as reddish fleabite spots which often within twenty-four hours rapidly pass through the stages of papule and pustule. The pustules may show umbilication and be either discrete or form large confluent areas with, later, ulcer or gangrenous formations. At times the eruption is limited to a few localized acne-like or pustular lesions, or it may be bullous or purpuric in character.

The nasal mucous membrane may be involved as the primary portal of entry of the infection, or during the course of the disease, and give rise to symptoms of a rhinitis with nasal obstruction. A thin, watery or mucopurulent irritating discharge, often blood-streaked, soon develops. About the bridge of the nose an erysipelatous inflammation, with vesicle and pustular eruption, appears and spreads over the face. The glanderous lesions in the mucous membrane lead to the formation of pustules, punched-out ulcers, and at times to the destruction of the septum, turbinates, or palate. The nasal sinuses are often involved in the process, and it may spread to the ear, causing a purulent otitis media.

By the further development or extension of glanderous formations the mucous membranes of mouth, pharynx, conjunctiva, larynx and trachea may become involved, giving rise to such symptoms as would direct attention to the location. There are few tissues which the glanderous process may not at some time involve. Thus we may also see arthritis—at times suppurative—periostitis, and osteomyelitis. The brain and meninges may be affected, giving rise to meningeal and, less frequently, to localizing symptoms.

With the onset of the local changes, or previous to its appearance, the disease is ushered in by a chill and a gradual or rapid rise of temperature. This continues along an irregular atypical course—at times being intermittent, remittent, or typhoid-like in character. The patient early complains of headache, backache and muscular pains. Joint pains are pronounced, and at times precordial and inguinal pains develop. Early prostration, out of all proportion to the amount of local involvement, is seen. Of gastro-intestinal symptoms, anorexia, nausea and vomiting are common, with later a severe fetid diarrhea. Respiratory involvement is indicated by aphonia and other symptoms of laryngitis, and when cough, expectoration, dyspnea and pleuritic chest pains develop, we can be certain of a pulmonary involvement. This is frequently bronchopneumonic in type, and caused by typical glanderous lesions scattered throughout the lungs.

During the early period of the disease the pulse may be rather slow in comparison to the temperature, but by the second and third week it becomes rapid, feeble and irregular, the heart showing other signs of myocardial weakness.

A mild stupor and insomnia are early cerebral symptoms. Later, delirium occurs, and preceding the fatal outcome, convulsions and coma. Emaciation and cachexia are pronounced, and death usually occurs within two or three weeks.

CHRONIC GLANDERS.—This form of the disease develops insidiously, and the local reaction may be so mild that the patient gives it but scant attention. For a few days the patient complains of slight fever, general malaise, headache, anorexia, slight arthritic and muscular pains, which subside, and the disease then runs a latent course. At other times the local reaction is more pronounced and of the phlegmonous or erysipelatous types, and occasionally it may be only a boggy swelling without inflammatory reaction. A few pustules or acne-like formations, with regional lymphadenitis, may appear and pass away without causing any pronounced constitutional disturbances. From some patients no history can be obtained regarding the site of primary inoculation.

Weeks or months after, the typical nodes appear in the skin, subcutaneous tissue and muscles, usually on the lower or upper extremities. They may be few in number and, as in the acute form, rapidly break down to form ulcers, abscesses and discharging fistulous tracts. The discharge is at first of the characteristic oily consistency, and later becomes purulent, due to secondary infection. These chronic processes often show a tendency to slow healing and, with the absence of constitutional symptoms, give the false impression that the disease has been arrested. However, rapid necrosis may again take place, and new nodes and abscesses appear. During these periods chills, sweats, temperature and muscular pains are present, and indicate an extension of the infection. The disease occasionally lights up, showing the constitutional symptoms mentioned, but no localizing symptoms. In other cases all the symptoms and signs are pulmonary, nasopharyngeal, or otherwise localized to an area showing a chronic glanderous process. The appearances of the local lesions are not diagnostic, and associated with the general symptoms the clinical picture may resemble many diseases. At any time during the course, the symptoms of acute glanders may develop. Cases have been known to remain latent for long periods, with at times only an occasional abscess appearing. Due to exposure, overwork, or an intercurrent infection, it again becomes active, or an acute outbreak terminates the case. The rash is always of grave omen.

When the mucous membrane is affected the same symptoms arise as were mentioned under acute glanders, except that the course is more protracted. An involvement of nose, mouth, pharynx, etc., may constitute the only local lesion present. The regional lymphatic glands are often involved and the process is frequently mistaken for a syphilitic manifestation.

The duration of chronic glanders may be from six weeks to as long as fifteen years. The usual duration is from four to five months. When the infection is limited to the site of inoculation and neighboring lymphatics the process may be arrested, but after the appearance of generalized phenomena, even though no further signs appear, it is impossible to say a cure has taken place.

Gaiger admirably describes his infection with chronic glanders, contracted from a pony. After the first attack he remained free from symptoms for a year and a half. Following an attack of malaria the latent infection again became activated.

LABORATORY FINDINGS.—An occasional leukocytosis with a relative increase in the polymorphonuclear neutrophils may be present. The urine frequently shows the presence of albumin and many hyaline and granular casts. Cases showing a transient glycosuria and an Ehrlich's diazo-reaction have been reported.

Diagnosis.—It is undoubtedly true that many cases of glanders go unrecognized. To quote from Robin's monograph: "Human glanders is not by any means the obsolescent disease that it is generally considered by the medical profession to be. It is probable that hundreds of cases annually find their way into the mortality records of the civilized countries of the world, classified as typhoid, septicopyemia, erysipelas, tuberculosis, syphilis, etc., which should properly be put down to glanders."

The history of exposure is important. A patient in contact with horses and showing indefinite symptoms, and particularly localized abscesses or other cutaneous or nasopharyngeal lesions, should be considered as a possible case of glanders. The manifestations of this disease are so protean as to simulate many conditions, and in addition to the diseases already quoted, it is often mistaken for influenza, rheumatic fever and variola. For the diagnosis the serological tests may be applied, using the proper controls, and injections of mallein have been employed with resulting typical reactions; but the basis of the diagnosis must rest primarily on finding the *Bacillus mallei.* For this the cultural methods advised, and the experimental inoculation of several male guinea pigs with the discharges and culture growth will, in the majority of cases, demonstrate its presence. In a case reported by Woodward and Clarke, showing no demonstrable focus, the bacilli were found in the urine. A positive blood culture will confirm the diagnosis.

Treatment.—PROPHYLAXIS.—The chief endeavor should be directed toward the **early diagnosis and eradication of the disease in horses.** This control is best maintained under government supervision. A diseased or suspected animal should be **isolated** and the other horses exposed to the infection quarantined. Specimens of blood should be obtained from all, and the **complement-fixation test** applied. For a detailed description of its application the article by Mohler and Eichhorn should be consulted. Briefly, it depends on the fixation of complement. "Serum producing complete fixation in 0.1 to 0.2 c.c. amounts, with no hemolysis, should be considered as glandered." The **ophthalmic test, injection of mallein** and **conglutination test,** are also valuable and satisfactory methods of diagnosis. The mallein gives excellent results when employed intradermally in the lower lid of the eye, and causes a pronounced local reaction in positive animals. An **agglutination reaction,** which like the complement-fixation tests depends on the production of antibodies in the blood, and is similar in principle to the Widal reaction, is also employed. It is less reliable, particularly in chronic cases, than the complement-fixation test and is considered positive when agglutination occurs in serum dilution of 1:1000 or over. All **horses giving negative reaction should be retested after a period of fifteen days,** in order to exclude those with a latent or subsequent infection, and all **glandered animals promptly destroyed.** In the employment of the various tests it is important to remember that injections of mallein and vaccines of the *Baccillus mallei* produce antibodies in the blood, which may persist for weeks and influence the serological test. **Stables in which glandered horses have been quartered should be thoroughly cleaned and disinfected.**

Extreme care should be taken by those in attendance on human cases of the disease. The **patient** is best **isolated.** A **sterile gown and rubber gloves** should be worn when dressing the lesions, and the **soiled surgical dressings destroyed.** The **linen, hypodermic needle, drinking vessels, etc., should be handled as infected articles.**

GENERAL MANAGEMENT.—Acute glanders runs its course uninfluenced by any therapeutic measures we command. **Symptomatic treatment** and the endeavor to **make** the **patient as comfortable as possible** comprises the extent of the treatment.

General treatment should be directed toward improving the general resistance of the patient. The usual **general tonics** may be given, but

rest, nourishing foods, and **agreeable surroundings** are of prime importance.

MEDICINAL TREATMENT.—In the treatment of chronic glanders many internal remedies, such as **potassium iodid, mercury and sodium benzoate,** have been recommended as exerting a favorable influence, but **they are without definite or permanent results.** Some observers have reported improvement following the injection of very small amounts of **mallein** at frequent intervals. This, however, should only be employed by those skilled in its use, as from its improper administration a chronic case may be converted into an acute type of the disease.

For nasal involvement douching with solutions of **boric acid** or **potassium permanganate,** and the application of **phenol** or **zinc chlorid** to the ulcers are advised.

SPECIFIC THERAPY.—The use of **serum from immune animals has been of no value.**

At the present time **vaccines of the Bacillus mallei** appear to give the most promising results in the treatment of the disease. An autogenous vaccine is given at frequent intervals, beginning with a dose of about five million and gradually increasing the dosage up to 200 million. With its use the temperature often falls, and healing takes place more rapidly and latent foci appear. When secondary infection with a pyogenic organism has occurred a combined vaccine may prove of value.

SURGICAL TREATMENT.—When local lesions indicate the presence of pus, or free drainage is otherwise indicated, the proper surgical measures are to be taken. Abscess cavities may be swabbed with **phenol,** followed by **alcohol.** Sinuses running beneath the skin should be laid open, the others drained and allowed to heal from below. For irrigating purposes **hydrogen peroxid, compound solution of cresol** 1 dram (3.75 c.c.) to the pint, or a **solution of tincture of iodin** (1:10), are useful. A wet **boric acid gauze pad** makes an excellent external dressing.

Prognosis.—Acute glanders and chronic types developing the acute manifestations are invariably fatal.

The mortality of the chronic glanders has been given as 50 per cent., but, according to Robin, this is too low a figure. He maintains that many cases recorded as cured should rightly be classified as probable cures. Due to the tendency of the disease to remain latent over long periods, it may again show active symptoms and go on to a fatal termination.

Pathology.—MACROSCOPIC.—In man, the glanderous lesions develop in the form of nodes, nodules, and areas of diffuse infiltration, which break down and form pustules, abscesses and ulcers. From the primary focus the infection spreads to the lymphatics and lymphatic glands, which also show nodular growth. Thrombosis occurs in the lymphatics and at times in nearby veins; and the further extension of the process is through the blood.

In addition to the areas of involvement previously mentioned, the *lungs* are invariably affected in the generalized process. Scattered nodes, varying in size, are found most frequently beneath the pleura. Diffuse greyish areas of infiltration, with surrounding inflammatory reaction, may be present, giving the appearance of a bronchopneumonia or lobar pneumonia. Chronic cases show a tendency for connective-tissue encapsulation of the individual nodes, and in the horse these often show a calcareous infiltration. The pleura shows thickening, and, like the other serous membranes, hemorrhagic areas. The *peritoneum* may be involved, and the cavity itself contain a serosanguineous fluid. As a result of long-continued suppuration amyloid changes are found in the *kidneys, liver* and *spleen*—less often do they show abscess or nodular processes. The liver and spleen may be enlarged. *Bone involvement* takes place usually by extension of a nearby process, but nodes sometimes appear in the marrow and periosteum. *Arthritis* is associated with a serous, serosanguineous or purulent exudate.

The *alimentary tract,* aside from the mouth and pharynx, is not often involved, and when ulceration occurs in the intestines the lymphoid tissue is spared. Involvement of the *brain* is also rare, but the meninges are occasionally involved in a localized pachymeningitis, and the sinuses sometimes contain a purulent collection.

MICROSCOPIC.—When the *Bacilli mallei* infect a tissue they give rise to the typical lesion which is classified as an infectious granuloma, and "wherever the location, the formation of the lesion of glanders remains the same." It consists of an accumulation of leukocytes and an epithelioid cell growth. The leukocytes undergo a rapid necrosis of the nuclear element, called chromatotaxis. This chromatin detritus is a peculiar characteristic of the glanders nodule, and retains the ability to take the various nuclear stains. The nearby lymph-spaces contain fibrin, and in the more chronic lesions there is proliferation of the surrounding fixed connective cells.

Historical Summary and Distribution.—Glanders, as it affects horses, is one of the oldest diseases definitely described by early medical writers. Aristotle, in the third century B. C., gave it the name *μήλις* and Apsyrtus in the fourth century A. D., impressed with its contagious character, recommended the segregation of affected animals. Vegetius, writing in the following century, also recognized its contagiousness and, although including other conditions, gave the first systematic description of glanders and farcy. Solleysel (1667) believed the disease could be conveyed through the air, and later French observers recommended the destruction of glandered horses and the disinfection of stables in which they were found. In Denmark, Abildgaard and Viborg, during the latter part of the eighteenth century, proved it was conveyed through the secretions and discharges from horses affected with glanders and farcy, and that the virus could be destroyed by heat and desiccation. Osiander (1783) was first to state that glanders could be transmitted to man, and Travers and Colman (1828) proved that horses could be infected from human cases. In spite of this evidence, pointing to the contagious and infective character of the disease, many physicians and veterinarians, in the early part of the nineteenth century, believed it was of a simple inflammatory and non-contagious nature. The merits of the two prevailing opinions were finally decided by experiments conducted under the supervision of the European governments. The result of the French Government test at the Alfort Veterinary School definitely proved the contagious nature of the disease. During the following period the disease in man was more frequently recognized, and two excellent descriptions of its manifestations appeared by Schilling (1821) and Rayer (1837). The specific organism was discovered by Löffler and Schülz in 1882, and the toxin, mallein, by Helman and Kalning in 1891.

Glanders, as it affects horses, is widely distributed throughout the world, and met with most frequently in certain civilized countries where horses are employed and confined in close quarters. From Europe and parts of Asia, where it prevailed extensively, it has been introduced by war and trade to the other continents. Extensive outbreaks in army horses are common occurrences during periods of war. It was introduced into the United States during the latter part of the eighteenth century and quickly spread to the western states. From the United States it was carried into Mexico and Cuba by the horses of the United States Army.

In those countries where government supervision for the eradication of the disease in horses is vigorously maintained human cases of infection are rarely encountered.

BIBLIOGRAPHY

Arms, B. L. Jour. Am. Med. Assn., 1910, lv, 591.
Bernstein, J. M., and Carling, E. R. Lancet, 1909, i, 319.
Cohen, B. Jour. Infect. Dis., 1919, xxiv, No. 1, 51.
Cramp, W. C. Jour. Am. Med. Assn., 1911, lvi, 1379.
Dudgeon, L. S., et al. Jour. Comp. Path. and Therap. 1918, xxxi, 43.
Gaiger, S. H. Jour. Comp. Path. and Therap. 1913, xxvi, 223; 1916, xxix, 26.
Government Publication. The ophthalmic and intradermic tests for glanders. U. S. Dept. Agric., Bureau Animal Indust., 1919.
Huidekoper, R. S. U. S. Dept. Agric., Bureau Animal Indust., 1917, A-13.
Hunting. A clinical treatise. H. W. Brown, London, 1908.
Kolle, W., and Hetsch. Die experimentelle Bakteriologie und die Infektionskrankheiten, 3d Ed., Vol. 1, p. 485.
Koranyi, F. V. Nothnagel's Spec. Path. u. Therap., 1897, Vol. V, Part v, 53.
Luborsch, O., and Ostertag, R. Ergeb. d. Allg. Path. u. path. Anat. des Menschen und der Thiere, 1902, p. 322; 1904-5, p. 300.
M'Fadyean, J. Jour. Comp. Path. and Therap., 1900, xiii, 55; 1905, xviii, 23.
Meyer, K. F. Jour. Infect. Dis., 1913, xii, 170.
Mohler, J. R., and Eichhorn, A. Am. Vet. Rev., 1913, xliv, 31.
——— U. S. Dept. Agric., Bureau Animal Indust., 1911, Bull. 136; 1914, Bull. 70; 1916, Bull. 166.
Nicolaier, A. Modern clinical medicine, Volume on Infectious Diseases, 872. Translation of Deutsche Klinik, 1905.
Robin, G. D. Studies from Royal Victoria Hospital. Vol. II, No. 1. Montreal.
Schoening, H. W. Jour. Agric. Research, 1917, xi, No. 3, p. 65.
Wade, E. M. Jour. Infect. Dis., 1913, xii, 7.
Woodhead, G. S., Allbutt and Rolleston. System of Medicine, 1906, ii, Part 1, 201.
Woodward, H. M., and Clarke, K. B. Lancet, 1913, ii, 1696.
Zeit, F. R. Jour. Am. Med. Assn., 1909, lii, 181.

PRACTICE OF MEDICINE—TICE

☛ **Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.**

CHAPTER XLV

HOOKWORM DISEASE

By C. C. Bass, M.D.

Etiology, p. 79:—Predisposing causes, p. 79; Exciting cause, p. 81—Symptomatology, p. 86:—Clinical history, p. 86; Physical findings, p. 90; Laboratory findings, p. 90—Diagnosis, p. 92; Complications, p. 93—Sequelæ, p. 93—Association with other diseases, p. 94—Treatment, p. 94:—General prophylaxis, p. 94; Individual prophylaxis, p. 95; Medicinal treatment, p. 95; Management of convalescence, p. 98—Prognosis, p. 98—Pathology, p. 99—Historical summary, p. 102—Distribution, p. 104—Sociological aspects, p. 105.

Etiology.—Predisposing Causes.—*Climate.*—Climate plays an important part in the occurrence of hookworm disease. It is a disease of *warm* climates, and becomes less frequent as the climate becomes colder. In those tropical countries where the weather is warm throughout the year, hookworm infection takes place during the entire year. In countries where there is a warm season and a cold season, little, if any, infection takes place after the cold season sets in. Hatching is delayed or prevented by cold and the unencysted larvæ are killed quickly by cold. The encysted larvæ, however, can endure low temperature remarkably well. In temperate climates where there is a warm season and a cold season, all other things being equal, infection becomes less as the length of the cold season increases.

Rain-fall and moisture have a great deal to do with the prevalence of hookworm. In dry countries, little transmission takes place, even though the temperature is favorable. This is due to the lack of the water and moisture necessary to favor the early life of the larvæ. Generally speaking, the greater the rain-fall, the more infection of hookworm takes place, provided other conditions are equal. A little rain every day, such as occurs during the rainy or wet season in many tropical countries, furnishes the most favorable condition.

Altitude.—So far as is known, altitude has no influence upon the prevalence of the disease except in so far as it may affect the climate or nature of the soil.

Soil.—The character of the soil is a most important factor in the spread of hookworm disease. Not only must there be warmth and moisture, but loose, porous, sandy soil is also necessary. Eggs hatch very poorly when mixed with a compact, clayey soil, and when they do hatch the larvæ usually die before they reach the encysted stage. They require oxygen to hatch, and the most favorable condition for hatching exists when feces containing the eggs are mixed with sandy soil. It is remarkable how the soil of a given region affects the prevalence of hookworm disease. For instance, in the state of Mississippi, in some of the hill counties in which the soil is sandy and favorable for hookworms, sometimes as much as 75 or 80 per cent. of the entire population are found to be infected, whereas in an adjoining delta county much of the soil of which is sticky and contains little or no sand, not even 5 per cent. of the population are found to be infected, and most of the cases found have been infected in other regions.

Sex.—Sex plays no part in the etiology of the disease except in so far as it affects exposure to infection. Darling has recently (1922) shown in different groups of people in the Malay States that men and boys have nearly three times as many hookworms as women and girls.

Age.—Hookworm disease is more prevalent in children than in older people, especially in the class of society in which the older children and adults wear shoes. Among people living in some of the poorer tropical countries, however, where adults go barefoot as much as children, the disease is just as prevalent in adults as in children. In the hookworm area of the United States, it is largely a disease of children, because most of the older people wear shoes. Where the disease is transmitted in mines, however, it affects the adult laborers. Not only do those who go barefoot contract it, but transmission also takes place through the hands, which are soiled by the infected mud left on the rounds of the ladders, etc.

Race.—Hookworm disease is less prevalent among the negroes than among the whites living in the same region. It is probable that this is not due to any racial immunity, but to a slight variation in habits which may favor infection in the one case and hinder it in the other. Barring whatever influence the habits of different races of people may have with regard to soil pollution and cleanliness, there is no evidence that there is any racial immunity to the disease. Any apparent difference in immunity is due only to this variation in habits.

Heredity.—Family predisposition actually plays a part. Not that the different members of a given family are more susceptible to infection, but the habits of certain families with reference to soil pollution and avoiding infection are much more favorable for the transmission of the disease than are those of others. Most of the hookworm infection contracted by children comes from other members of the family. In this case, as in many other diseases, an infected individual is a much greater source of danger to the members of his own family than he is to other people.

Individual Susceptibility and Personal Conditions.—There is no individual susceptibility and no personal condition that especially favors infection, so far as is known, except of course any special factor which might cause the individual to be particularly exposed to infection.

Social Conditions.—Generally speaking, the higher the social condition, the less does hookworm disease occur. It is largely a disease of the poor. On account of the lowered vitality and earning power, the hookworm subject is poor and unable to obtain education and to provide those things which others have and which tend to protect against infection, for instance, shoes, sanitary living conditions, etc.

(*a*) *City versus Country.*—Hookworm disease is largely a disease of the country and not of cities and large towns. Even in small towns in the more civilized countries there is little transmission of hookworm disease. Small towns and villages in the less civilized countries, where there is very little or no provision against soil pollution, are very favorable for spread of the disease. The more concentrated the population, if no provision is made against soil pollution, the more favorable are the conditions for infection, because individuals are exposed to probable infection not only by the members of their own families, but also by others living in the group.

(*b*) *Occupation.*—Those occupations which expose the individual most to sources of infection are naturally the most favorable for the transmission of the disease. Working in mines not equipped with suitable means of preventing soil pollution is one of the occupations especially favoring disease. In the southern part of the United States, the disease is more prevalent among the agricultural class of people, simply because less provision is made by them against soil pollution. The work of Darling and his co-workers in Malay, Java and Fiji emphasizes the influence of occupation upon the worm index. Those whose occupations exposed them most to infection have much higher indices.

Previous Attack.—A previous infection in a given individual makes it more likely that subsequent infections will occur. Not only is the individual liable to subsequent infection by others, but he is more likely to be a source of infection himself. A soil pollutor is more likely to return to places he has polluted himself than are others, and personal or individual habits may favor extensive reinfection.

EXCITING CAUSE.—*Bacteriology: the Organism.*—The hookworms that infect man belong to the class *Nematoda*, family *Strongylidæ*, subfamily *Strongylinæ*, genus *Uncinaria*. Two species have been recognized and identified throughout the world: *Ankylostoma duodenale* (the Old World hookworm) and *Uncinaria americana* (the New World hookworm). There are many other species which infect the lower animals, such as dogs, cats, cattle, sheep, seals, monkeys and others, but none of these are known to infect man, nor do the two species which infect man infect the lower animals, so far as is known. *Ankylostoma duodenale* is the most prevalent species in European countries and in many Asiatic countries. The New World species prevails almost exclusively in the Western Hemisphere, in Africa, and in many other parts of the world. In some regions both species are found, the *Ankylostoma duodenale* predominating in one locality, and the *Uncinaria americana* in another.

(*a*) *Morphology.*—The general appearance of both species is almost exactly the same and no differentiation can be made by casual observation. Males of *Ankylostoma duodenale* are about 10 mm. long and 0.45 mm. wide. The females are from 12 to 18 mm. long and 0.60 mm. wide. In both sexes the anterior end tapers gradually. In the female, the posterior end tapers to a fine point or spine. The posterior end of the male tapers slightly for the last quarter of its length, but the tip of the tail is concealed by the bursa, which flares out to a width equal to that of the thickest part of the body or even wider. The color of living worms is flesh-red or cream color. The posterior two-thirds are often brown or reddish-brown from the blood in the intestines. The head bends backward, resembling a hook, and this is supposed by those not informed to give rise to the name "hookworm," but as a matter of fact, the term is derived from certain rib-like structures in the tail of the male worm.

The mouth parts of hookworms are complicated, and furnish features by which the different species are differentiated. The following description, copied from Dock and Bass, may be of interest.

"The mouth of the Old World worm opens toward the back of the parasite, on account of the dorsal bend, so that the rim of the mouth is nearly or quite parallel to the long axis of the body of the worm. The mouth capsule, or 'buccal capsule,' is of half-oval or cup shape, the anterior axis curved and long, the posterior shorter and nearly straight. The bottom of the mouth cavity is flat, uneven, and nearly transverse to the long axis of the animal. Seen from the front, the mouth is somewhat longer dorso-ventrally than laterally. The framework of the mouth is made up of a number of chitinous plates, or, according to Looss, of a continuous plate with suture-like depressions, giving it rigidity, but permitting changes of shape, such as are demanded by the function of the mouth, and especially holding on to or letting go the mucosa of the host. The shape of the opening varies much with the degree of dilatation of the orifice at the time of examination or fixation. On the ventral side of the capsule, just within the cavity, are two pairs of sharp-pointed, curved, hook-shaped teeth; at the base of the capsule, on the ventral side, two triangular pointed teeth, or 'lancets,' and on the front of the dorsal part two tooth-like structures separated by a fissure. 'Beneath the buccal rim the lining of the cavity is thrown into six papillary prominences, characteristic of the entire group.' (Smith.) In the middle of the dorsal wall of the mouth capsule is the orifice of the duct of the dorsal esophageal gland. From the hook-shaped ventral teeth, the so-called cervical glands extend almost to the middle of the body."

The males of *Uncinaria americana* are from 6 to 10 mm. and the females from 8 to 15 mm. long. Their natural appearance is well illustrated in Fig. 1 from Dock and Bass.

While the *Ankylostoma duodenale* has two buccal teeth, the *Uncinaria americana* has only one dorsal conical tooth. The mouth capsule is smaller and lobular, and the orifice is somewhat quadrated.

The eggs of the two species resemble each other very closely, but those of *Uncinaria americana* are slightly larger. The difference, however, is not sufficiently great to permit of differentiation by the appearance of the eggs, nor can they be differentiated in the larval stage.

When feces containing hookworm eggs are properly diluted, either with sandy soil or with some other substance which favors the action of

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

oxygen and is exposed to favorable temperature and moisture conditions, hatching takes place in from twenty-four to forty-eight hours. Hatching does not take place unless the feces are properly diluted, except perhaps on the surface of the material. After hatching, the larvæ move about through the material and feed on the feces. In about five days, under favorable conditions, they become encysted. During the period before encystment, they are easily killed by chemicals, drying, sunshine, etc. Shade, therefore, is almost essential for their growth. In fact, too much dilution of the feces also results in the death of the larvæ, perhaps because of lack of food.

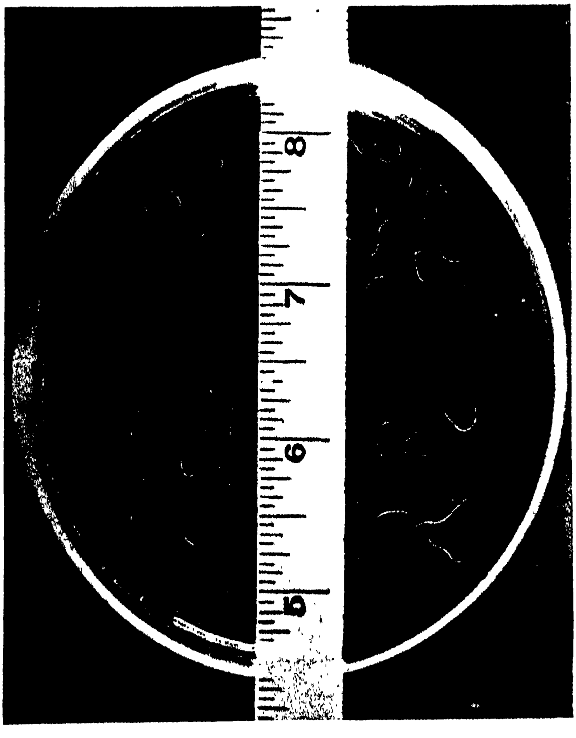


Fig. 1.—Necator Americanus.
Upper part males, lower half females. Inch measure.

The encysting of the larvæ consists in the loosening of the outer skin. The larva remains within this skin, or sheath. The mouth parts seem to be sealed hermetically and feeding ceases. As a matter of fact, most of the larvæ that hatch are destroyed by unfavorable conditions before they reach the encysted stage. Only a small proportion reach this stage. This, however, is a very resistant stage and encysted larvæ have lived for more than a year under favorable experimental conditions in the laboratory. Augustine, of the Johns Hopkins School of Hygiene group of investigators, has shown, however, that under natural conditions, in

Trinidad, W. I., at least, they rapidly disappear and the extent of their life is limited to about six weeks. During all of this time they are capable of infecting any victim on whose skin they may find lodgment.

Looss believed that only the encysted larvæ survived and were infective. Cort and his co-workers have more recently shown that infested soil contains both ensheathed and unensheathed larvæ, sometimes more than 50 per cent. being unensheathed. Moreover, they believe that these continue to live in the soil and are capable of infecting, the same as the ensheathed ones.

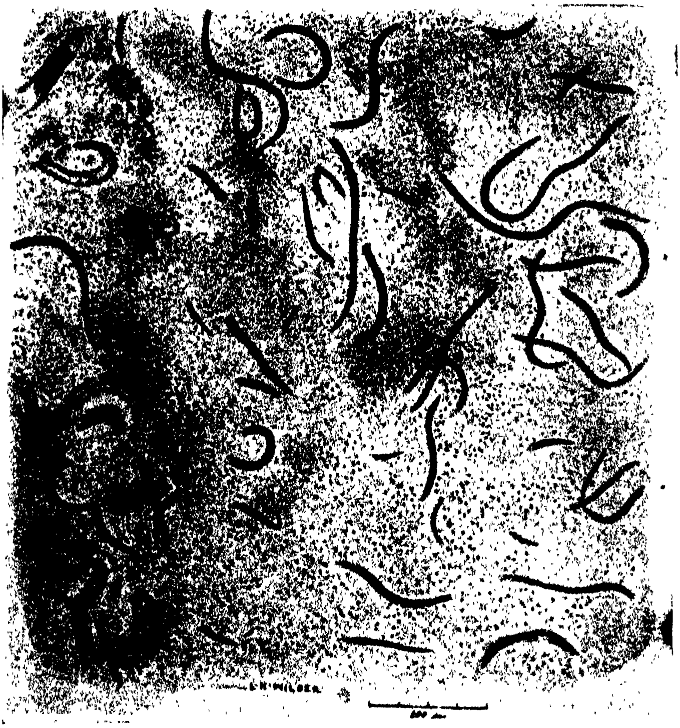


FIG. 2.—SECTION OF SKIN AS SEEN UNDER THE MICROSCOPE, SHOWING THE HOOKWORM LARVÆ CRAWLING THROUGH THE SKIN. (After Stiles.)

The mature larvæ remain in the mud and water in which they have developed. It is supposed that they remain rather quiescent and inactive unless disturbed. Whenever they are disturbed, however, they become very active and move about quite rapidly. If mud and water containing infective larvæ come in contact with the feet or other parts of man, the larvæ rapidly penetrate the skin. It has been found that they can enter the skin within four minutes from the time they are applied.

(*b*) *Distribution.*—(1) *In the Body.*—In this stage they seem to possess wonderful ability to burrow through tissue. The manner in which

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

the larvæ enter the body through the skin cannot be described more impressively than by the classical and almost diagrammatic photomicrograph (Fig. 2), after Stiles. After a larva enters the skin, it burrows until it finally enters a small vein, and from there it is carried by the blood-current to the heart and thence to the lungs. It is stopped in the lungs by the capillaries and usually breaks its way through the capillary wall, producing a small hemorrhage into the lung tissue. When large numbers of larvæ are applied to experimental animals, like, for instance, the guinea pig, the damage done to the lungs results in the solidification of the lungs or parts of the lungs by blood. Sections of such experimental material show large numbers of larvæ to be present.

Other larvæ reach the lymph-vessels and are carried to the lymphatic glands, but probably finally reach the lungs. Once in the lungs, the larvæ soon enter the bronchial tubes and gradually pass up into the trachea. No doubt many of them are expectorated with sputum that may be coughed up. Many others, however, are swallowed. The habits of different individuals with regard to spitting may contribute very largely to the throwing off or reduction of the larvæ at this stage. There is the great possibility and, in fact, the author thinks the probability, that the individual habits here suggested may make a great difference in the number of worms finally reaching maturity in two individuals infected with an equal number of worms.

Larvæ that are swallowed pass through the stomach, resisting the gastric juice, and finally reach the small intestine, where they penetrate the mucosa. Usually a small blood-cyst forms around the larva in the tissues, and in a few days it begins to grow. During the next three or four weeks, at least one and possibly two other ecdyses occur, a skin being shed each time. A few days, perhaps from five to ten, after a larva reaches the small intestine, a buccal capsule is developed and mouth parts corresponding to those of the adult are acquired. After sufficient development, they are capable of attaching themselves to the mucous membrane and grow rapidly. Adult size is reached in about eight weeks from the date of infection. The worms begin to produce eggs in about six weeks from the date of the infection.

The length of time the adult worms may live in man does not seem to be well established. Opinions vary in estimating the period at from about one to seven years. Hookworm subjects who avoid further sources of reinfection begin to improve noticeably in from one to three years. This does not necessarily mean that the life of the worms is that short, but perhaps the improvement is a result of the dying off of the older worms.

(2) *Outside of the Body.*—There is little danger of infection through *drinking water*, because of the fact that it would seldom occur that water so grossly contaminated with human excrement as to contain hookworm larvæ would be drunk.

Food is not likely to be a source of infection, but may be so under exceptional conditions. If, for instance, raw food like lettuce, radishes, strawberries, etc., is grown on grossly contaminated soil and eaten without being thoroughly washed, it might be a source of infection. The encysted larvæ have a tendency under certain conditions to crawl up on vegetation, such as blades of grass, etc., which may lead to the contamination of such vegetables.

(*c*) *Modes of Conveyance.*—(1) *Contamination of the Soil.*—As has already been pointed out, the infection is generally conveyed by infected soil which sticks to the bare feet, or by the contact of infected material with the skin in some other way. The chief mode of infection is by wading in mud and water, barefoot, or even with shoes on. The only other very extensive source of infection is through the hands, and possibly also through the feet, in miners. Hookworm ova swallowed by chickens and pigs pass through the alimentary canal (Acker, and Acker and Payne) and will hatch. These animals may be important spreaders of the infestation in certain instances.

(2) *Carriers.*—The hookworm carrier is to be considered as a menace not only to himself, but also to others living in close association with him. He is, however, not dangerous to others except to those who permit themselves to be infected. The carrier is much more dangerous to himself than to anybody else, except perhaps his own immediate family. Even moderate infection is sufficient to give rise to enough larvæ to infect others. It has been estimated that one female worm may produce as many as two thousand eggs in one day.

Infection may vary in degree from very slight to very severe—*i.e.*, to the number of worms necessary to destroy life. No doubt, in cases of very heavy infection, many people die as a result of the damage done to the lungs—causing pneumonia, etc.—without the cause being suspected. It is not known at present what proportion of the larvæ that enter the skin succeed in establishing themselves and reaching adult life in the intestines. It is quite probable that many are eliminated, not only by being expectorated in the sputum, but perhaps in other ways.

Symptomatology.—If we appreciate the fact that hookworm infection may be accompanied by the presence of a number of worms varying from one to several thousand, or sufficient to produce death, we recognize that the symptoms produced by hookworm infection must vary very greatly in different individuals. Not only is there great variation as a result of the very different number of parasites present, but there is great variation in the reaction of different individuals to the same degree of infection. One individual will show much more marked symptoms in the presence of a mild infection due to perhaps one hundred parasites than another one would who is infected by several hundred or possibly a thousand. Many of the symptoms produced by the disease, especially when the infection is light, are so mild that they are not recognized as symptoms of disease. That they are actually produced by the infection can frequently be demonstrated, however, by treating the patient and observing the disappearance of these symptoms.

CLINICAL HISTORY.—The voluntary clinical history of most hook-

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

worm patients, if any history at all indicating the infection is given, is usually that of more or less anemia of long duration, weakness and palpitation upon exertion and, in the case of heavy infections, retarded development in growing children. A very common history is simply that of being "puny" for a long time.

Further inquiry elicits a history of attacks of "ground-itch" in almost all cases of heavy infection acquired in the usual way. Those who are infected in mines and tunnels usually give a history of having had erythema and itch on the hands and arms. In the severest cases, especially those of long duration, there will usually be a history of dropsy and great weakness, and sometimes of leg ulcers, appearing from time to time for a period of years. The history usually indicates that these conditions are worse in the spring of the year.

In a certain proportion of cases the subjects admit having a capricious appetite, and many of them say that they have acquired the habit of eating dirt, salt, coffee-grounds, etc. Many others, however, even though they have acquired such habits, deny them, either from shame or, in the case of children especially, from fear of chastisement.

Symptoms of Incubation Period.—It is perhaps most appropriate to speak of the period from the time at which the larvæ enter the skin to the development of the worms in the intestinal canal to the egg-producing age, as the incubation period. This period is about six weeks in duration. However, after an individual is once infected, he usually carries the infection for many years, during which period additional infection occurs from time to time. Of course, some of the worms die. After the first infection, the incubation period of subsequent infections overlaps the disease produced by previous infections.

The first symptoms of the incubation period are those of ground-itch. Usually the infection is on the feet, but it may be on any other part of the body which is exposed to contaminated material. More infection takes place between the toes than on the surface of the feet and toes, because of the fact that infected material is more likely to be retained there for a long time. A stinging, pricking sensation is felt in a few minutes after infectious material is applied to the skin. If very small numbers of larvæ puncture the skin, the symptoms are less marked, but if the infecting larvæ are numerous, the symptoms are more severe. These local symptoms appear so promptly following the infection that most persons who suffer from severe ground-itch recall the time infection occurred and frequently the particular pool or location in which it was contracted.

Within a few hours of infection there is an itching and burning sensation, accompanied by redness and perhaps by more or less edema. Within twenty-four hours small vesicles appear. There is probably one vesicle at the site of penetration of the skin by each larva, but it frequently occurs that the vesicles are so numerous that they are more or less confluent. Whenever the infection is heavy enough, these confluent vesicles lift considerable parts of the skin, which later may come off in rather large pieces, especially between the toes. Sometimes, in very heavy infections, thick, heavy layers come off the soles of the feet.

In from thirty-six to seventy-two hours from the time the infection takes place, the vesicles usually become pustular, if they have not been broken by scratching. The desire to scratch is irresistible and most of the vesicles and pustules are broken sooner or later. Usually a crust forms on the parts which are allowed to dry. Many a little country boy, in regions where hookworm disease prevails to a great extent, has spent restless nights because of the ground-itch.

The process runs its course in from about five to eight days, unless prolonged by excessive damage by scratching, etc. The exudate becomes less, and the scabs dry and come off, leaving new, tender skin beneath, just as would occur in other superficial vesicular and pustular processes.

In mild infections probably few respiratory symptoms occur. In very heavy infections, however, during the first ten days following the infection, there is more or less cough, due to the irritation and damage to the lungs produced by the larvæ passing through them. These symptoms usually pass unnoticed or at least are not connected with the ground-itch.

Vague gastro-intestinal symptoms have been recognized as occurring after the second week of the six weeks' "incubation period." These are rather indefinite and consist more or less of slight pain and uneasiness, especially in the epigastrium.

In very mild infections, none of the above described symptoms may be recognized. On the other hand, in the event of overwhelming infection, it is very apparent that they might be much more intense, and that even death might result from the condition produced by the action of thousands of larvæ passing through the lungs and burrowing in the intestine.

Symptoms During Progress of Disease.—Most of the symptoms of hookworm disease are not characteristic of this disease only, nor are they diagnostic. *Anemia* is produced in all cases in which the number of worms is sufficient. It may vary from a slight anemia, that cannot be demonstrated by any of our present methods, to a very severe condition. This anemia is quite apparent, and in severe cases gives to the patient's eyes more or less of a fish-like glare. In cases of heavy infection of long duration there is a dirty-yellow tinge to the skin. There is more or less *weakness* upon exertion, largely dependent upon the amount of anemia, sometimes accompanied by more or less dizziness. As a result of the weakness, which is greatly intensified by exertion, the patient does not exert himself as willingly as otherwise, and is frequently called lazy on account of this attitude. Hookworm disease is sometimes called the "lazy disease." The subject is, however, not lazy, but sick and weak.

If the infection and the resultant anemia persist for many years in children, they *fail to develop physically and mentally* as rapidly as they otherwise would. In many instances much dwarfing is produced in this way. A child fifteen years of age will perhaps not be larger than he should be at seven or eight. There is retardation of puberty. The picture copied from Publication No. 5 of the Rockefeller Sanitary Commission shows, in a striking way, the dwarfing effect of the disease (Fig. 3).

In the severest cases, there is great weakness and *edema* of the feet and ankles, and sometimes severe anasarca is seen. There is *dyspnea* on slight exertion, and *bruit de diable* of the jugulars. In these severe cases, there is sometimes a tendency to *dilatation* of the *pupils* and blurred vision.

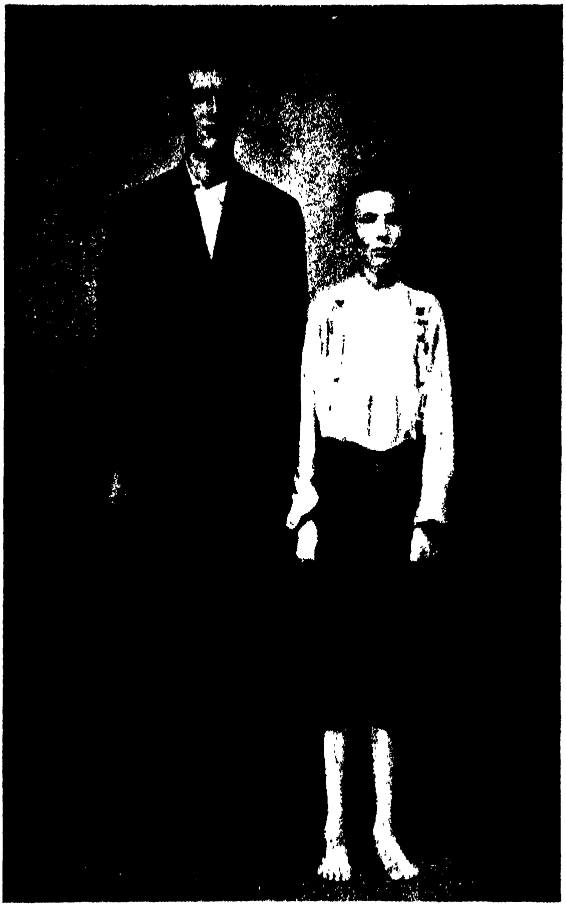


FIG. 3.—PHOTOGRAPH SHOWING DWARFING EFFECT OF THE DISEASE.

These boys are brothers. No. 1, age 17, weight 156 pounds; light infection. No. 2, age 18, weight 74 pounds; heavy infection.

The *appetite* is usually good and often enormous. A capricious appetite often develops, and the patient eats unusual things in an unconscious effort to satisfy this demand of nature for some element or substance greatly needed. The habit of eating dirt—geophagy—is often developed. Some children, and even adults, eat large quantities of clay—the so-called clay-eaters or dirt-eaters.

Fever is not commonly produced by hookworm disease, except in the case of heavy infection and rather severe anemia. Many such patients have a maximum temperature of 101° or 102° F. (38.3° or 38.9° C.) during a part of or throughout the day.

PHYSICAL FINDINGS.—The "tallow-faced," "pot-bellied" clay-eater of hookworm regions is easily recognized, and would be suspected as a hookworm subject by any one familiar with the disease. Anemia of more or less intensity can be recognized in those in whom the infection is sufficiently great. It is not recognizable, however, upon observation in the moderate and very mild cases. Whenever the infection is sufficiently great and has existed for a sufficient length of time, the dwarfing in children may be recognized and lead to a suspicion of the presence of the disease. Pulsation of the great veins is very noticeable in those with severe hookworm disease.

In severe cases the hair usually feels dry and dead, and the skin dry and parched. There is reduced perspiration and oil secretion.

Upon percussion, dilatation of the heart can be made out in severe cases, but in mild cases nothing is demonstrable.

Upon auscultation, the bruit in the neck veins and usually a hemic heart-murmur can be made out. This is nearly always true of those cases in which dropsy is present.

LABORATORY FINDINGS.—*Blood.*—Two definite changes are found in the blood in patients suffering from hookworm disease, provided the infection is sufficiently great—anemia and eosinophilia.

The *anemia* varies in intensity with the amount of infection, but may become very grave. It is of the secondary or chlorotic type, the color index always being below one. The disease is sometimes called Egyptian chlorosis on account of the anemia and of the fact that it is very prevalent in Egypt. Both the hemoglobin percentage and the red blood-cell count are reduced, but the hemoglobin is reduced more rapidly or further from the normal. In extreme cases it is reduced to as low as 15 or 10 per cent., but usually death occurs early in the cases with such severe anemia. The red-cell count seldom, if ever, is as low as a million cells, but it is frequently below two million. There is little or no stippling of the red-cells and few, if any, nucleated cells are found. The total leukocyte count is not greatly affected, if at all.

In most cases the *eosinophil count is increased* more or less, according to the number of worms present. The tendency is for the eosinophil count to increase as the infection increases, up to a certain point. It may reach 30 per cent., seldom more. If the infection continues to increase and the case becomes worse, the tendency is for the eosinophil count to decrease, and most very severe cases have a lower count than do the less severe cases. Usually, before death, the count falls to the normal average or below. It has been suggested that this is the result of the exhaustion of the ability of the eosinophil-producing tissue of the body to respond to the constantly increasing demand for eosinophils.

Urine.—The urine is normal in moderate or mild hookworm infection, but in the severe form, especially when accompanied by anasarca, there is more or less albumin present. In the worst cases it may reach 40 or 50 per cent. of moist albumin by the Purdy ferricyanid test. Casts are not commonly present.

Feces.—Tests of the feces for occult blood are nearly always positive, even in mild or moderate infections. This is due to the fact that there is more or less blood wasted by oozing at the site of the bites made by the worms in feeding.

(*a*) *Microscopical Examination.*—The presence of the *eggs* of the worms is shown by a microscopical examination. The proper method of examination for all ordinary purposes is to secure a small sample of the normal stool, dilute a quantity about the size of a match head in a drop of water on a microscope slide, and examine under the low power microscope. If sufficient worms are present to give rise to clinical symptoms of disease, one or more eggs will almost certainly be found in such a preparation. It is better to examine two or three such preparations, but generally several eggs will be found in one preparation if the infection is sufficient to cause symptoms. A small number of worms, and also the ingestion of alcohol and drugs which may cause a temporary reduction in the number of eggs produced, may result in failure to find them in every instance in which infection exists. For practical purposes, however, this method is sufficient.

To make an absolutely certain negative diagnosis, it is better to use the centrifuge method. One way of applying this method is as follows: Dilute a quantity of feces, at least two or three grams, with several times the quantity of water, strain through gauze to remove coarse particles, and then centrifuge properly so as to collect in the bottom of the tube any eggs that may be present. Many who undertake to do this fail to recognize the fundamental principle involved and do not succeed well. The principle is that the eggs are larger and heavier than most of the material in suspension and therefore are thrown to the bottom more quickly. The centrifuge should run just long enough to throw the eggs to the bottom of the tube and no longer. One should learn the length of time required for the particular centrifuge used if he is to succeed with this method. Usually it will be only a few seconds. Pour off the supernatant fluid, add enough water to bring the contents of the tube to the former level, mix thoroughly by shaking, and centrifuge again. Pour off the supernatant fluid as before. Shake the tube so as to mix the remaining contents in the bottom with the drop or two of fluid that remains, and pour this out on a slide for examination. The tube must be thoroughly shaken in order to procure the sediment which contains the eggs, as there is a tendency for them to stick to the bottom of the tube.

Stoll, in a recent thorough study in Porto Rico, has found the average

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

daily output of eggs of female hookworms to be about 8,000 or 9,000, corresponding to about 44 eggs per gram of formed feces per female worm, about 25 per gram of mushy feces and 12 per gram of diarrheic feces. Therefore, there are on an average 12 to 44 eggs per gram of feces for each female worm. One who possesses the proper technical ability with the centrifuge should be able to find one or more eggs in any specimen if the patient harbors even one producing female worm. The writer knows that this opinion differs from that of others with wider experience in examination of feces, who find that a good many cases of light infection are missed by them.

The eggs are oval, with broadly rounded poles. The shell is colorless, measuring from 0.056 mm. to 0.072 mm. in length, and from 0.034 mm. to 0.038 mm. in width. The eggs of the New World hookworm are slightly larger than those of the Old World hookworm, but both fall within these extremes. In fresh stools, the nucleus is usually in four segments. There is a distinct, clear, albumin-filled space between the shell and yolk from one-eighth to one-fifteenth as wide as the diameter of the egg. As the specimens become older, the number of segments increases until finally, in from twenty-four to forty-eight hours, embryos have developed within the shell. These are likely to hatch out in specimens kept under favorable conditions, giving rise to motile larvæ (Fig. 4).

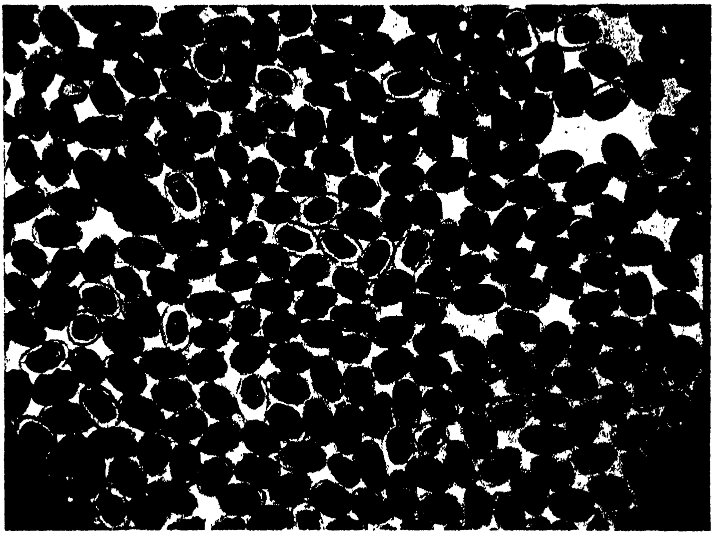


Fig. 4.—Preparation Made by Bass Method from Feces. Seen through 1/6 objective.

Diagnosis.—The *clinical history* may indicate hookworm disease, and in all cases in which there is history of long-standing anemia, dwarfing, capricious appetite, etc., the disease should be looked for. However, definite diagnosis is to be based upon laboratory findings and nothing

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

else. The history of ground-itch indicates very strongly the presence of hookworm disease, but it is not such a clear-cut condition as to serve as a basis for an absolute diagnosis of hookworm.

Physical findings, such as anemia, weakness, cardiac dilatation, etc., unless otherwise explained, call for examination of the stools for hookworms. Some enthusiasts have thought that they were able to diagnose hookworm disease upon observation and superficial physical examination. Although it is possible in hookworm regions to pick out the bad cases in many instances, this method of diagnosis should never be resorted to and should never be followed to the neglect of the more dependable microscopical examination of the feces.

The *laboratory findings* determine the presence or absence of hookworm infection. Thorough, competent examination, when the findings are negative, excludes hookworm infection, and finding the eggs, of course, makes it certain that hookworm infection exists. It may be associated with many other diseases and conditions. It is therefore important that one should not make the mistake of attributing the condition of a patient to hookworm disease alone when other diseases may be present as well.

Complications.—Among the worst complications of hookworm disease are the general anasarca and the accompanying albuminuria and leg ulcers. The first condition indicates more or less damage to the kidneys and is of special importance because of the fact that the specific drugs employed in the treatment of hookworm infection are more or less damaging to the kidneys. This renders it necessary to employ the life-saving remedies with more caution and perhaps less expedition than would otherwise be done.

The leg ulcers occur in cases of severe anemia of long duration, and usually of more or less anasarca. On account of the thick scar-tissue surrounding the ulcers, they sometimes heal very slowly, even after the worms have all been removed.

Sequelæ.—No permanent sequelæ result from hookworm disease except the physical and mental dwarfing that occurs in those who are severely affected during and throughout the developmental period. We have no exact data as to just how nearly such patients may approach their normal development after the removal of the parasites. It is not uncommon for an individual eighteen or twenty years of age to have developed no more than a normal child does by the age of twelve or fifteen. If the infection is relieved, rapid growth, both physical and mental, takes place. The author has seen one boy of fifteen years gain twenty pounds in weight and grow two inches taller in one month following the removal of hookworms. Captain J. F. Siler had one patient who gained thirty-five pounds in one month. The writer knew one man who was relieved of his hookworm disease chiefly by changing his environment, and who grew several inches after he was twenty-seven years of age. It is the writer's belief, however, that those who have not eliminated their infection before they have reached the age of about twenty, never grow to the size that they would otherwise have attained.

In fact, he is inclined to think that unless infected persons are relieved of their infection by the age of fifteen or sixteen years, they may not reach their full physical development. The deficiency might not be recognized as due to the hookworm disease, however, because of the great variation in the size of different individuals, which results from many other influences, recognized or unrecognized.

Association with Other Diseases.—Hookworm disease may be associated with any other disease or condition occurring in regions where it exists. In many regions, a large percentage of all the population, as much as 50 per cent., 75 per cent. or even 90 per cent., are infected. In such regions it would be associated, in a corresponding proportion, with other diseases that occur. When it is associated with either acute or chronic disease in which all of the vitality of the patient is needed to aid him in his fight against it, hookworm disease may very largely control the outcome. Let us consider, for instance, a case of pneumonia or typhoid in a hookworm subject who has perhaps 50 per cent. hemoglobin. Theoretically, at least, the patient's chances are not as good as if he did not have the hookworm disease. In a case of tuberculosis in a hookworm subject, it is quite certain that the chance of recovery is not as favorable as if the hookworm infection did not exist. And yet, in the event of death, in all such instances, the death would be charged to the other disease and not to the hookworm, although without it recovery would, perhaps, have occurred.

Treatment.—General Prophylaxis.—Soil pollution is the means of transmission of hookworm infection, and therefore **provisions against soil pollution** prevent the disease. If all the people in a given region would use sanitary privies, there would be no transmission of hookworm infection. Whenever this is neglected, provided other conditions are favorable, the disease is likely to be spread to a corresponding extent. Disinfecting all infected individuals would also result in preventing the spread of the disease in any given locality. A combination of both of these measures would lead to even more rapid results. If the spread of the disease were entirely stopped, it would still be several years before all infected persons would lose their infection without treatment. If they are treated, on the other hand, they escape the one or more years of sickness which would otherwise result.

The regions where hookworm disease is prevalent are those in which there are few **sanitary latrines.** There have been many demonstrations of sanitary improvement for the purpose of controlling hookworm disease, but the recent one given by Dr. P. G. Pope, in Harrison County, Mississippi, under the Department of Rural Sanitation of the Mississippi State Board of Health, has been one of the most complete and extensive demonstrations ever made. The entire county, having a rural population of about seven thousand, was worked on the intensive plan. Of the 1,549 homes in the county, only 56.2 per cent. were found on first inspection to have latrine accommodations. On the last inspection every home in the county, or 100 per cent., had them. In addition to providing for the introduction of latrines into all the homes, Dr. Pope ex-

PRACTICE OF MEDICINE—TICE
Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

amined 60.8 per cent. of the population for hookworm infection. It was found that 55.1 per cent. of these were infected, and 100 per cent. of the infected were given treatment. Thus within a period of one year, by following the plan developed especially by the International Health Board and other agencies with which they have coöperated, after many years of experience, hookworm disease has been practically wiped out and conditions have been established by which it is assured that it will not return.

Individual Prophylaxis.—Individual prophylaxis consists in **avoiding infection.** In almost all cases of hookworm disease occurring in rural sections, the infection takes place through the feet, as a result of going barefoot. **Wearing good shoes** protects against infection.

Medicinal Treatment.—We have three outstanding specific remedies for hookworm disease—thymol, oil of Chenopodium, and carbon tetrachloride. Their effectiveness, dose for dose, seems to be carbon tetrachloride first, oil of Chenopodium second, and thymol last or least.

A single treatment with either carbon tetrachloride or oil of Chenopodium will remove 95 to 100 per cent. of the worms present. A single treatment with thymol frequently does not remove more than 70 to 90 per cent. of the worms. Whatever the drug used, the treatment may be repeated in a week or ten days to remove any worms that may have escaped the first treatment.

Thymol Treatment.—For the best results to be obtained from thymol, it is necessary that the alimentary canal be empty, at least that portion in which the worms are situated. This is accomplished by a **saline purgative, preferably magnesium sulphate.** Unless the alimentary canal is empty, the worms are protected from the action of the thymol by the intestinal contents and also by the more or less tenacious mucus which surrounds them.

(*a*) *Dosage.*—The following table, copied from H. H. Howard,* gives the proper doses of thymol and magnesium sulphate for persons of different ages. The solution of magnesium sulphate referred to is made by dissolving 15 pounds of the salts in 3 gallons of water. Two drams contain about 1 dram of magnesium sulphate.

Table 2. Dosage of Thymol and Magnesium Sulphate Solution.
(H. H. Howard.)

Apparent Age of Patient	Dose of Thymol	Dose of Magnesium Sulphate Solution
1 to 5 years	3 to 5 grains (0.195–0.324 grams)	2 drams (7.50 c.c.)
6 to 10 "	10 to 15 " (0.650–0.972 ")	4 " (15 c.c.)
11 to 15 "	15 to 30 " (0.972–1.95 ")	6 " (22.5 c.c.)
16 to 20 "	30 to 45 " (1.95 –2.92 ")	8 " (30 c.c.)
21 to 50 "	45 to 60 " (2.92 3.9 ")	12 " (45 c.c.)
Over 50 "	30 to 45 " (1.95 –2.92 ")	12 " (45 c.c.)

(*b*) *Mode of Administration.*—A dose of magnesium sulphate is given on the night before the thymol is to be administered. The patient should eat no supper that night and no breakfast the following morning. Early in the morning one-half of the dose of thymol is administered, and in two hours the other half. Two hours after the last thymol is taken another dose of magnesium sulphate is given. The object of this latter is to hasten the elimination of the thymol and to prevent its absorption. It has served its purpose after it passes through the duodenum and jejunum and the sooner it can be eliminated, the sooner absorption is stopped.

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* See H. H. Howard. The Control of Hookworm Disease by the Intensive Method. Publication No. 8, International Health Board.

(*c*) *Frequency of Administration and Duration of Treatment Necessary.*—The course of thymol should be repeated about once a week until the patient has been disinfected. This can be demonstrated by a microscopical examination. Two treatments will remove all the worms in at least 50 per cent. of the cases, and in those in which some worms still remain, at least 90 per cent. are found to have been removed. In rare instances, six or eight treatments may be required before all the worms are destroyed.

More frequent administration than once a week is usually not harmful, but results in a certain amount of irritation of the kidneys, in some cases at least, and especially in the cases with anasarca. The only way to determine definitely when a patient is disinfected is by the examination for hookworm eggs. The final examination should be made at least two or three weeks after the last treatment, as thymol tends to stop egg-laying temporarily.

(*d*) *Preparation of Thymol for Administration.*—The best method of preparing thymol is to break it up into a rather coarse granular condition (not a fine powder) and mix it with an equal quantity of sugar of milk, and then to fill into capsules. The sugar of milk serves the purpose of preventing the thymol from packing, which it otherwise tends to do.

(*e*) *Contra-indications.*—Conditions which contra-indicate the use of thymol, or at least suggest caution, are acute febrile diseases, diarrhea, dysentery, gastritis, organic cardiac or renal disease, pulmonary tuberculosis, general anasarca, old age, pregnancy, etc. Patients with such complications should be treated with smaller doses and under favorable conditions for observation and treatment of any untoward symptoms that may arise.

(*f*) *Thymol-poisoning.*—Absorption of a considerable portion of the dose of thymol may produce muscular weakness, vertigo, slight cyanosis and slowing of the pulse-rate and respiration. If a larger amount is absorbed, and in the case of especially susceptible persons, there may be collapse.

To relieve mild symptoms, all that is necessary is to **put the patient to bed** (in fact, patients should in any case remain in bed during the administration of the thymol) and to **empty** the **alimentary canal** by means of enemas. In the case of more severe symptoms, when collapse is present, **morphia** 1/6 grain (0.01 gram) with **atropin** 1/50 grain (0.001 gram) should be given. **Strychnin** is also useful to counteract the collapse. The most important thing is to empty the alimentary canal. Even the use of the **stomach pump** may be of service in some cases.

Treatment with Oil of Chenopodium.—(*a*) *Dosage.*—The Uncinariasis Commission to the Orient, of the International Health Board, made a comparison of the Chenopodium and thymol treatment of hookworm disease in the Orient.* A part of the summary of their conclusions is as follows:

> It would appear from the comparisons given that the half-maximum dose (0.5 c.c. three times, or 1.5 c.c.) of oil of Chenopodium is the treatment for recommendation as a routine vermicide.
>
> It does not have the toxic effects of the full dose, and two treatments have the very satisfactory result of removing 99 per cent. of all worms present.
>
> It has the additional advantage of a more uniform action, a greater effect on ankylostomes, and of being less unpleasant to take than thymol.
>
> Thymol shows an advantage over this half-maximum dose of oil of Chenopodium in that the 90 grains (5.83 grams) dosage produces a better result when single treatments are compared. This advantage disappears, however, when two half-maximum treatments of oil of Chenopodium are given.
>
> Smaller doses compare unfavorably with a single half-maximum dose of oil of Chenopodium. A dose as large as 90 grains of thymol, if administered indiscriminately throughout the population, would probably give rise to serious symptoms.

(*b*) *Mode of Administration.*—The routine method of administering Chenopodium recommended by this commission is to allow a light evening meal, followed by a purgative dose of magnesium sulphate. The next morning at 7, 8 and 9 o'clock, 0.5 c.c. or 8 minims oil of Chenopodium are given, making a total of 1.5 c.c. The last dose of Chenopodium is to be followed in two hours by a purgative dose of magnesium sulphate. The Chenopodium is best administered in the regular hard gelatine capsules. The soft gelatine capsules are not as good.

(*c*) *Duration of Treatment Necessary.*—The course of treatment should be repeated about once a week as in the case of thymol.

(*d*) *Contra-indications.*—Practically, the contra-indications against the use of Chenopodium are the same as those against thymol.

(*e*) *Chenopodium-poisoning.*—Whenever Chenopodium is absorbed, it has a toxic effect, and if absorbed in sufficient quantities, causes death. A number of deaths have been caused by less than the dose of 3 c.c. usually given as a maximum. In order to lessen absorption and therefore to lessen the toxic action, a good many omit the preliminary purgative and allow a full meal at night. Some even permit a meal on the morning on which treatment is to be given.

Chenopodium produces more or less heat or burning in the stomach, or colicky pains, and nausea and vomiting sometimes occur.

If much of the drug is absorbed, there may be numbness and a tingling sensation in the extremities, headache, vertigo, tinnitus aurium, muscular weakness, incoördination and spasm, delirium, convulsions and coma. These symptoms come on rather slowly, sometimes even two or three days after the drug has been taken. In extreme cases of the condition, with convulsions and coma, death is likely to occur.

Perhaps the most important treatment for Chenopodium-poisoning is a rather large dose of **castor oil.** The oil seems to reduce and prevent further absorption and to hasten elimination. The application of **heat** externally, and **stimulants** are indicated in the cases of collapse, but there is no specific remedy.

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* See Jour. Am. Med. Assn., Feb. 23, 1918, lxx, 499.

Treatment with Carbon Tetrachloride.—Carbon tetrachloride for the removal of hookworms was first proposed in 1921 by Hall. Since that time it has been extensively tried in many of the large hookworm control projects in different parts of the world. The reports indicate that for hookworm it is somewhat more effective even than oil of Chenopodium, a single treatment removing more than 95 per cent. of the worms (Smillie). It is non-effective against ascarids and other worms; neither is it effective against such intestinal protozoa as Giardia, Trichomonas, Chilomastix, Endolimax, etc. (Hogue and Van Winkle).

Dosage.—The dose of carbon tetrachloride should not exceed (3 c.c.) for an adult and proportionate doses for children. Much larger doses have been given without any harm. However, more recent reports have shown that even this amount may destroy life.

Mode of Administration.—No preliminary purgative or fasting is necessary. Giving the full dose at one time seems to be as effective as divided doses. It may be filled into capsules just before administration or it may be floated on a spoonful of water.

Contra-indications.—The contra-indications for thymol and oil of Chenopodium apply to carbon tetrachloride as well. Alcoholism seems to be a special contra-indication. Even 1.5 c.c. is dangerous and may produce death in alcoholics.

Carbon Tetrachloride-poisoning.—Symptoms of poisoning are dizziness, nausea, headache, and somnolence. These are usually transient. Fatty degeneration of the liver similar to that produced by chloroform is found at autopsy in fatal cases and in experimental poisoning in animals.

MANAGEMENT OF CONVALESCENCE.—In most hookworm cases the patient may be allowed to proceed with his usual occupation during convalescence. In extreme cases, it may be several days and possibly even a few weeks before he should be allowed to resume regular physical activity. Plenty of nutritious food and fresh air favor the rebuilding of the blood, which has been deficient for so long.

It is uncertain whether any drug or drugs hasten recovery from the anemia. It takes place at a very rapid rate, in any case. The author does not believe that any drug treatment should be employed, although iron is probably not harmful.

Prognosis.—AS TO RECOVERY.—Barring extremely rare and severe cases, proper treatment is followed by prompt recovery. In the very severe advanced condition there is always the extreme possibility that death may occur before the drug has time to act, and the infection can be reduced. Unfortunately, in these very severe cases, the specific remedy itself is not without possible harm and must be employed somewhat guardedly.

The *mortality* from hookworm disease varies greatly in different regions. Where the disease is very prevalent and where it runs its course untreated, many deaths are directly caused by it and still more indirectly. Ashford and King, of the Porto Rico Anemia Commission, estimated that the death rate, before systematic treatment was begun, was 30 per cent. This was during the early studies of the disease, and no doubt the writers had in mind principally the severe form of infection. As has been indicated, hookworm disease produces many deaths indirectly. Persons with other diseases, which in themselves might not be fatal, die as a result of the combined effect of the particular disease, plus the devitalizing hookworm infection.

As to Function.—Whenever a hookworm subject is disinfected, he rapidly returns to the normal, except in instances where the disease has existed for many years during the developmental period of life, in which case he will not be able to reach full development physically, and possibly not even mentally. The question of development depends very largely upon the age of the individual when he is relieved of his infection. The younger a person is when he is relieved, the more likely he is to reach full development.

Pathology.—At autopsy, the *skin* of a hookworm subject is found to be pale, sallow, or even lemon color and waxy in appearance. There is no emaciation in most cases, subcutaneous fat being well preserved and usually pale or yellow in color. The omentum and pericardium often contain an unusual amount of fat.

The *muscles* are pale, soft and bloodless. Serous effusions are usually present in the serous cavities, especially in the abdomen.

There is, generally, enlargement and dilatation of the *heart.* The heart-muscle is flabby and pale. Ashford and King noted sclerosis of the arteries, even in young children.

Sandwith found the *spleen* enlarged in one-third of his autopsies in Egypt. It is possible, however, that this may be due to associated conditions, such for instance as malaria, for other writers have not found spleen enlargement in subjects dying of uncomplicated hookworm disease.

The *kidneys* are pale and large, but there is no cast formation in the tubules.

No remarkable change occurs in the *liver,* although it is pale, greasy looking and brittle.

The *stomach* is frequently large, as a result of excessive eating. Hookworms have occasionally been found in the cavity of the stomach, and Gutierrez found several attached to the mucosa. Butterworth * reported a most remarkable case in which a girl, eight years of age, had a hair ball or cast in the stomach, made up largely of hair and of different kinds of fibers. This was a severe case, in which the capricious appetite led to the ingestion of material that could not be digested or passed on through the alimentary canal.

In severe hookworm infection, one finds large numbers of free worms and others attached to the mucous membrane of the *duodenum* and *jejunum.* Most of the worms are found within four feet of the stomach. If the autopsy is postponed more than a few hours after death, the chilling of the subject, as well as perhaps other influences, kills the worms.

The intestinal contents are usually blood-stained and consist largely of mucus. The *intestine* should be opened carefully and spread out on a flat surface without washing. There are large numbers of ecchymotic and eroded spots over the mucous membrane. These vary from 3 to 4 mm. in diameter, or are even larger. In some cases they are very numerous, giving a speckled appearance to the mucosa, as stated by Whipple. In the midst of the red area is a small, pale elevation where the worm is attached, or marking the site from which one has recently been detached. Worms and lesions are sometimes found in the ileum, as well as higher up.

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* See Jour. Am. Med. Assn., Aug. 21, 1909.

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

In some autopsies, from a few hundred to even three or four thousand worms may be found. In others, comparatively few worms are found in cases of death undoubtedly due to hookworms. Sandwith has suggested that in these severe cases "the half-starved worms are dislodged by purges or by repeated attacks of diarrhea."

The ecchymotic spots at the site of attachment of worms sometimes have minute erosions or ulcers in their centers. Microscopical examination of material taken from near the site of the bites usually shows blood-cells. There are a larger number of bites than of worms, showing that they move from place to place over their feeding ground; each time, however, they no doubt remain attached for a considerable length of time. Sandwith found 250 worms and counted 575 bites in one case. Sections of lesions produced by the bites show infiltration of the tissue with large numbers of eosinophils. We have here the explanation for the increase of the eosinophils in the circulating blood. There is a call or demand for eosinophils to perform whatever function they do perform in the tissue surrounding the bites, and nature furnishes an increased supply in the circulating blood to be carried there for that purpose.

Sometimes rather large ulcers are produced and in a few instances perforations and adhesions have been found.

Just how the worms produce the extreme anemia has been a subject of considerable discussion, and it is possible that we do not even yet recognize all of the factors that enter into its production. One thing usually overlooked in considering this phase of the subject is the probability that the large amount of damage, inflammatory condition, etc., in the intestinal mucosa may largely prevent its normal function. Looking at a heavily infected specimen, one may recognize the improbability that such tissue can function in an even approximately normal manner. Malassimilation and malnutrition resulting from this condition may contribute largely to the production of the anemia.

The manner in which the worm attaches itself to the mucosa cannot be described in any other way as well as it is shown in the accompanying classical and almost diagrammatic photomicrograph by the late Dr. W. M. Gray, Washington, D. C., taken from the report of the Porto Rico Anemia Commission, 1906-07. (Fig. 5.) Many of the worms found at autopsy contain more or less blood. Some of them are stuffed so full of it that they appear deformed. Practically all of them contain some blood. The amount of blood consumed during the twenty-four hours by several hundred or a few thousand worms would be considerable. The loss of such an amount only once or a few times would not produce any considerable anemia. It would promptly be replaced. However, when even small quantities of blood are lost every day over a long period of time, marked anemia is produced.

Not only does each worm draw a considerable amount of blood when it feeds, but when it moves to another place, the site of the bite continues to bleed for hours afterward. It is probable that the total amount of blood lost in this way is much greater than the amount actually taken in by the worm. There is so much lost that the intestinal contents are frequently of a chocolate brown color or even reddish. Lower down they become tarry in appearance. Even small numbers of worms give rise to enough hemorrhage to produce positive occult-blood-tests. Ernst and Leichtenstern and also Whipple have observed that when living worms are removed and placed in water they throw out of their mouths at intervals clouds of red blood-cells. This probably explains the observation sometimes made that worms found in autopsies on subjects that have been dead for many hours may not contain any blood-cells. Even the structure of the worm itself indicates that sucking is an important function.

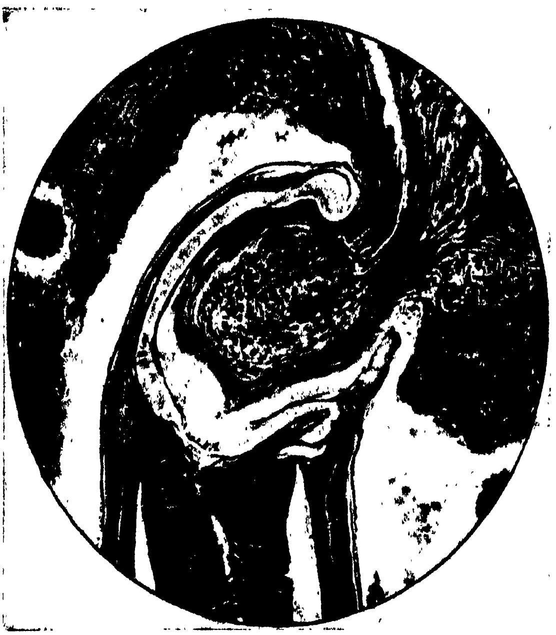

FIG. 5.—PHOTOMICROGRAPH OF UNCINARIA AMERICANA SUCKING MUCOSA.

By the late Dr. W. M. Gray, Washington, D. C., from a report of the Porto Rico Commission, 1906-1907.

Another event that is no doubt of importance and may contribute to the production of anemia is the secondary infection which must take place at the site of the bites of the worm. The presence of large numbers of such infected lesions for a long period of time should certainly be a fruitful source of harm.

It is thought by many that the introduction of a toxic substance by the worm may cause or at least contribute to the cause of the anemia. Attempts to isolate the poison of hookworms have not met with success. It has also been suggested that perhaps the decomposition of the blood excreted by the worms and of that which flows from the bites may play some part in the chain of events.

Historical Summary.—No doubt hookworm disease has existed for thousands of years, but its specific cause was recognized less than a century ago. In 1786, an epidemic of what was called "miner's anemia" broke out in Schemnitz, Hungary. Many other epidemics were described from time to time, but the specific cause of this miner's anemia, or miner's chlorosis, had not been discovered. It was charged to climate, vitiated air, etc.

In 1838, Dubini, in Milan, found worms in a woman who had died of pneumonia. At that time, he thought that these worms had not been previously discovered. Later he found them in at least 20 per cent. of the bodies examined, sometimes associated with other worms. He proposed for them the name *Agchylostoma*, meaning "bent mouth." Bilharz, in 1853, and Griesinger, in 1854, in Egypt, recognized the relation of hookworms to the extremely prevalent "Egyptian chlorosis" which was the cause of a large proportion of the deaths in that country. In 1866, Wucherer, in Brazil, called attention to the disease, and interest gradually increased in other tropical regions.

The discovery by Grassi and Parona in 1877, of the diagnostic value of the ova in the feces really marked an important advance in our knowledge of the disease and, especially, of its prevalence. Intense anemia was noted among the workers in the St. Gothard tunnel in 1879-1880, and hookworms were found to be present in all the cases without any other cause of the disease being discoverable.

One of the very prominent symptoms of severe hookworm disease—dirt-eating—has been recognized and frequently discussed in the southern part of the United States for at least a hundred years.

In 1895, Allen J. Smith found ova of hookworms in the feces in a water-closet in Galveston, Texas, and, in 1901, he recognized a hookworm that was different from the *Ankylostoma duodenale*, in an individual from Melbourne, Australia. In 1901, Dr. Charles Wardell Stiles published his views,* stating that hookworm infection in man must be more or less widespread in the United States. Smith also found the ova in the stools in 8 cases out of more than 80 medical students in the Galveston Medical School. To him belongs much of the credit for directing the attention of the medical profession to the presence of the disease in the United States.

To Stiles, however, must be given much of the credit for the recognition of the importance and widespread distribution in this country. To him, the trained zoölogist, the discovery of a few victims here and there meant that the parasite must be widespread. Among the early workers to contribute much to our knowledge of the disease in this country were Claude A. Smith and H. F. Harris. They made many valuable observations, and the work of Smith, by which he demonstrated the manner in which infection takes place and is manifested in the form of ground-itch, was especially valuable. Bailey K. Ashford, in 1899, and later Ashford and King, reported finding hookworm disease in Porto Rico. Later, in 1904, a commission consisting of Ashford, King and Pedro Gutierrez was appointed to study and treat the anemia disease among the Porto Ricans. Their reports in 1904, and subsequently, constitute most valuable contributions to our knowledge of the disease.

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* See Texas Medical News, July, 1901.

Largely as a result of the activities of the earlier workers in this country, the Rockefeller Foundation became interested in the control of the disease in the United States. A fund of one million dollars was first provided, and later this was increased to five million dollars. This fund was expended by the Rockefeller Hookworm Commission during a period of five or six years, in efforts to direct attention to the importance of the disease and also to furnish treatment for the millions of victims in the southern states. Much good was accomplished by the efforts made in the eradication of the disease. Much more valuable, however, was the store of information gained to the effect that the disease is much more widely prevalent than was at first thought to be the case. Methods of treatment and prevention were also found.

At the same time, some information was gathered as to the occurrence of the disease in other parts of the world. Some idea was gained of the menace which this disease constitutes to the mental and physical development of the human race in a wide zone encircling the earth. What it means to civilization was appreciated by the Rockefeller Foundation. The period for which the Rockefeller Hookworm Commission was organized having expired, the Rockefeller Board created the International Health Board, to include in its activities hookworm work, not only in the United States, but throughout the world. By coöperating with organized health agencies, and by contributing a part, and sometimes a very large part of the funds involved, they have made demonstrations of hookworm control in many countries and have been responsible either directly or indirectly for the treatment and relief of hundreds of thousands of hookworm victims.

Of even more importance than the relief that has been furnished to a large number of people, is the educational work directed against soil pollution. It is absolutely impossible to estimate, and it is difficult to comprehend the amount of sickness and suffering, due to hookworm disease and other soil pollution diseases, from which the world has been saved by the work of the International Health Board, the outgrowth of the Rockefeller Hookworm Commission. Not only has much disease been prevented up to the present time, probably very much more than has been treated or cured, but the propaganda and the demonstrations made will lead to continued benefit in this direction for many years, even though the activities of the International Health Board should cease.

PRACTICE OF MEDICINE—TICE

☛ Remove from Volume V pages 79–105 inclusive and insert therefor these New Pages, 79–105 inclusive.

To emphasize the idea of future benefit which must result from the work done against hookworm disease, encouraged and supported more or less by the International Health Board, the author would again point to the demonstration of rural sanitation conducted by the Mississippi State Board of Health, under Dr. P. G. Pope, Field Director, in Harrison County, Mississippi. Examination of over 4,000 people living in the county showed that 55.1 per cent. of them had hookworm disease. They were all given treatment. The first survey made of this county showed that only 56.2 per cent. of the homes had sanitary latrines. The last inspection showed that 100 per cent. had them. Not only have most of those in the county who had hookworm disease been cured, but conditions have been established whereby any who may not have been disinfected, will not be a source of transmission to others. Hookworm disease, and, in addition thereto, the several other soil pollution diseases, have been, therefore, practically wiped out in the county. The results of the work already done will no doubt last for many, many years, whether or not anything further is done. Just that sort of work, although perhaps not always so perfectly successful, is being done in many countries throughout the world at the present time, and is destined to grow and produce untold good for an indefinite time in the future.

Distribution Throughout the World.—Hookworm disease is distributed in a belt encircling the globe, extending from about 38° N. latitude to 35° S. latitude. All other things being equal, it is most intense as the equator is approached. There are many small areas in which the disease may exist outside of this belt under special conditions, as, for instance, in mines. There are also many localities within this belt in which the disease is not prevalent. Climate, moisture, and the habits and customs of the people, contribute very largely to its distribution in any given country. It frequently happens that in a certain section of a country the infection may be very heavy, and that a section only a short distance away may be practically free from it. In the more highly civilized countries, as the United States, the disease is not extremely prevalent except in the rural sections.

Economic loss resulting from hookworm disease is absolutely beyond comprehension, especially in some of those countries in which the disease is so prevalent. Throughout the world, millions upon millions of people are having their very life-blood sapped day after day for months and years, lowering their vitality and ability to accomplish labor or to develop mentally as they should and would otherwise develop. Thousands are dying as a result, either directly of the disease, or indirectly of the lowered vitality produced by it, rendering them unable to withstand the inroads of other diseases which they could otherwise throw off. Consider for a moment a group of laborers, like, for instance, miners or others who have, as a result of the disease, not more than 50 per cent. of the normal amount of hemoglobin. They are laboring under a great disadvantage all the time, and it is absolutely impossible for them to perform anything like the labor which they could accomplish if they had their normal strength. If we could but realize that many, many millions of people are now laboring daily under this handicap, and could only compute the actual reduction in efficiency and put it in suitable terms, we would be astounded and bewildered at the daily tribute the world pays to this disease. That it is of primary importance, no one can question.

Sociological Aspects.—Generally speaking, the higher the social position, the less prevalent is the hookworm disease. Poverty leads to conditions favorable to the disease, and it in turn leads to poverty. Among the mining population the disease is more prevalent among the men than among the women and children. This is the case wherever standards of living are low and civilization is less advanced. In the United States, on the other hand, the children are more often infected than the parents. A man or woman marrying a hookworm carrier is more likely to become infected than if a non-infected person were selected. Living in close association with hookworm cases in the home and in the fields increases one's chances of having it himself.

PRACTICE OF MEDICINE—TICE

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CHAPTER XLVI

HODGKIN'S DISEASE

BY ARTHUR F. BYFIELD, M.D.

Definition, p. 107—Historical survey: nomenclature, p. 107—Etiology, p. 110:—Predisposing causes, p. 110; Exciting cause, p. 111:—Nature of the disease, p. 111; Mode of conveyance, p. 116—Symptomatology, p. 116:—Brief survey of the clinical picture, p. 116; Symptomatology in detail, p. 121—Diagnosis, p. 131:—Differential diagnosis, p. 133—Clinical types, p. 138—Treatment, p. 141:—Medicinal treatment, p. 141; X-ray and radium therapy, p. 143; Surgical treatment, p. 144; General and symptomatic treatment, p. 145—Prognosis, p. 145—Pathological anatomy, p 146.

Definition.—A fragmentary definition of Hodgkin's disease is all that is possible at the present time. The consensus of opinion labels it an infectious granuloma due to a specific microörganism. In its various stages, it produces characteristic histological pictures which constitute the most stable part of our knowledge of the condition. Clinically, the majority of the cases run a typical course, characterized by a slow, painless, progressive enlargement of the lymphatic nodes of the body, beginning with those of the cervical chains. The generally symptomless period of the early lymph-node hyperplasia gradually goes over into a second phase, during which the adenopathy becomes more or less universal; other organs—spleen, liver, etc.—become involved, and anemia and cachexia supervene. There is no well-authenticated case of permanent recovery, hence the oft employed synonym *malignant granuloma*, and the belief still held by not a few observers that the disease is to be included among the malignant tumors rather than among the infections.

The outstanding feature of the present-day conception of Hodgkin's disease as an entity is the histopathology of the affected nodes, upon which alone a positive diagnosis—in the light of current knowledge—can be made. It cannot be too strongly emphasized that to-day a correct point of view with reference to this disease demands two essentials: that is a sharply delimited member of the large group of lymphadenopathies and that a positive diagnosis can rest only upon a definite histopathological basis.

Historical Survey: Nomenclature.—A clear understanding of what is meant by Hodgkin's disease necessitates a brief survey of the history of the subject. Such a survey is valuable and instructive also because of the light it throws upon the complicated field of the generalized lymph-node enlargements.

An historical review may be conveniently divided into two periods, the first embracing the years 1832 to 1898, the second extending from the latter year until the present time. As a subdivision of the second period may be regarded the recent revival of interest in the subject centering about the etiological significance of a pseudodiphtheria bacillus (*Bacterium hodgkini*).

The first period began with the publication (1832) of Hodgkin's work "On Some Morbid Appearances of the Absorbent Glands and Spleen." Despite the abundant literature of this period, we may say that but little progress was made toward the obtaining of data which, to-day, we consider essential to a proper appreciation of the condition. The one illuminating exception was the contribution of Virchow (1845), who separated, from the large group of the lymphadenopathies, one with characteristic changes in the blood (lymphatic leukemia); yet, as we shall see, this great step forward needed further analysis, i.e., in the matter of those leukemias with little or no increase in the white blood-corpuscles of the circulating blood—the so-called aleukemic leukemias—before its significance with reference to Hodgkin's disease could be understood.

For the remainder of this initial period there is little to be commented upon except the multiplicity of synonyms which arose, each expressing the view of the particular writer as to the nature of the condition he was discussing. The "nature of the condition he was discussing" is used advisedly, as a perusal of the literature indicates very clearly that the Hodgkin's disease of these observers—or rather the various synonyms employed by them to denote what in their respective opinions was the essential pathology—was still merely a large ill-defined group of generalized lymphatic-gland enlargements and not the well-demarcated picture which at present, and with good reason, we call Hodgkin's disease. (We are uncertain even of the true nature of the 7 cases described in Hodgkin's original treatise.) In other words, granting that our own conception of the nature of the disease is correct, it would be quite impossible to make use of these older cases to determine, for statistical purposes for example, which were Hodgkin's disease in the strict sense and which were clinically similar, but histologically quite dissimilar, conditions. This will be more fully brought out in the section on Differential Diagnosis, which is based, to a great extent, upon the modern refinements of investigative methods.

It seems desirable to enter somewhat in detail into these writings of the last century, because a good understanding of this particular phase orients one, not only as to the place occupied by Hodgkin's disease in the large domain of the lymph-node hyperplasias, but also as to the specificity of the Hodgkin's process. In addition, the fitness of the name Hodgkin's disease becomes apparent. And, as already stated, one cannot expect to have a clear-cut idea of the significance of this process unless one understands, on the one hand, how it has gradually been dissected out of the heterogeneous group of lymphadenopathies and, on the other hand, that the term Hodgkin's disease is the only appropriate name for the entity under consideration.

If one bears this in mind a partial recapitulation of some of the terms formerly used to describe the disease—or rather the disease group—will be found highly instructive. Bonfils (1856) spoke of it as a cachexia without leukemic changes (*cachexie sans leucémie*). Virchow (1865) allied it with the lymphosarcomata. Much confusion was caused by Cohnheim's use of the term pseudoleukemia (lymphadenoma without leukemic changes). The majority of observers perhaps regarded the condition as some form of malignancy, as is evidenced by such descriptive terms as *malignant lymphoma* (Billroth, 1869), *malignant lymphosarcoma* (Langhans, 1872), *reticulated desmoid carcinoma* (Schulz, 1874), *malignant aleukemic lymphadenoma* (Orth, 1887), and *gland sarcoma* (Langebeck). Such names as *syncytial endothelioma* (Ciaccio) and *reticular desmoid carcinoma* indicate that the hyperplasia of the reticular tissue was early recognized as a significant histological change. Pel and Ebstein's *recurrent glandular fever* also belongs to the terminology of this period.

One comes almost inevitably to the conclusion, from reading this literature of this first period, that, although some of the cases were Hodgkin's disease in the modern sense, many were of a widely dissimilar nature—other granulomas, aleukemic leukemias, lymphosarcomata, etc.

Although the correct evaluation of the term *pseudoleukemia* belongs properly to the later historical period, it may suitably be considered at this time. The name was first employed by Cohnheim to denote that large group of lymphadenopathies formerly loosely called Hodgkin's disease. It differs from the many other synonyms used at one time or another to denote that condition by the fact that it has persisted to a large degree up to the present time. On many sides we still hear the terms Hodgkin's disease and pseudoleukemia used interchangeably. In the light of our present conception of Hodgkin's disease this is certainly an error. If pseudoleukemia has any place in scientific terminology it should be used to denote that form of lymphatic leukemia which shows the usual and characteristic changes in the lymph-nodes and other lymphatic tissues, but which is unassociated with an increase in the total number of white blood-corpuscles in the circulating blood (although exhibiting a relative increase in the number of lymphocytes). Even when thus employed, the term has little scientific justification, because the above condition is not a pseudoleukemia but a true leukemia, and is better described as an aleukemic, or alymphemic, leukemia.

The second historical period, corresponding to the present century, comprises the greater part of the research which has given us a definite histopathological picture of the disease; it includes in the process, also, the immense amount of work bearing upon the etiological relationship to the morbid process of the tubercle bacillus and, more recently, of a diphtheroid bacillus, phases of the subject which will be discussed in their proper places. (*See* Etiology: Exciting Cause, p. 111.) Briefly stated we have learned in this second period that pseudoleukemia is not a scientifically appropriate name for Hodgkin's disease, and that the large group of generalized lymph-node enlargements can be divided into three distinct sub-groups; the granulomata (which include Hodgkin's disease, tuberculosis and syphilis), the true neoplasms, which are chiefly of a sarcomatous nature, and the leukemias. Finally, in view of that fact that the granuloma which we are considering is apparently a disease *sui generis,* we cannot do better than employ, for the time being at least, a term against which there is no valid objection, namely Hodgkin's disease.

Etiology.—PREDISPOSING CAUSES.—As contrasted with the exciting causes of the disease, the predisposing factors are reasonably well established, particularly in a negative way.

Sex.—As to the question of sex, observers are generally agreed that the condition occurs in men two or three times as frequently as in women. Expressed in percentages, it occurred, in Ziegler's 220 cases, in 67.7 per cent. in males and in 32.3 per cent. in females; in Longcope's series of 86 cases, in 67.4 per cent. in males and in 32.6 per cent. in females; among Gower's 100 collected cases, in 75 per cent. in males and in 25 per cent. in females; and in other tabulations there was a similar sex distribution of cases.

Age.—The age incidence is equally well defined. The preponderance of cases occur in young adults and in middle-aged individuals. About one-third of the cases appear before the twentieth year and about one-half between the twentieth and fortieth years. After the age of forty, statistics show a rather rapid decline in the frequency of occurrence. Although the condition has been observed at practically every period of life, it is extremely uncommon in infancy and old age. The literature records the extremes of occurrence as five and one-half months and seventy-six years.

The author quotes Ziegler's table based upon 220 collected and definitely established cases to show the accepted sex and age incidence:

TABLE I. SEX AND AGE INCIDENCE IN HODGKIN'S DISEASE

Age (Years)	Sex		Total Number of Cases	Percentage of Cases Based on Whole Series
	Male	Female		
1-10	20	16	36	16.4 (22)[1]
11-20	25	12	37	16.8 (17)
21-30	32	19	51	23.2 (27)
31-40	36	14	50	22.7 (18)
41-50	19	5	24	10.9 (10)
51-60	13	3	16	7.3 (4)
61-70	4	2	6	2.7 (2)
Totals	149	71	220	100.0

[1] The figures in parenthesis are based upon Ziegler's personal cases.

Occurrence.—As to the geographical distribution of the disease, it occurs in a sporadic way in all parts of the world, sparing no race. Practically all of the reported cases, however, are from European and American sources. Although not to be reckoned among the common diseases in the matter of *frequency,* it is hardly a rare condition and is observed as often as the leukemias, if not more often.

Heredity: Family Predisposition.—In so far as our present knowledge goes, these factors play no part in the etiological basis of the disease. Several isolated instances of the disease in the same family are rather to be regarded as coincidences.

Individual Susceptibility.—Susceptibility based upon a particular habitus is probably not an etiological factor. In fact, it is a striking thing that the greater number of cases appear insidiously in individuals of robust constitution, previously in apparently good health; indeed, the general health often remains surprisingly good even though the case has reached the second, or generalized, stage.

Social Conditions.—No blame can be attached to faulty social conditions. The disease is just as likely to occur among the rich as among the class exposed to *filth, overcrowding, bad ventilation, poor lighting and allied conditions,* and occurs among urban as well as among city dwellers. As may readily be inferred from the foregoing, *occupation* is likewise of no moment etiologically.

Previous Disease.—The various other recognized predisposing causes may be dismissed very briefly in so far as they are related to Hodgkin's disease: none apparently plays a rôle. In particular, no importance can be attached to the predisposing effect of previous disease, including tuberculosis, nor does a tuberculous family history seem to be of any significance. The question of tuberculosis in its relation to Hodgkin's disease, and that of infections in various parts of the head as forerunners of the disease, will be considered elsewhere in this article.

EXCITING CAUSE.—*The Nature of the Disease.*—The exciting cause of Hodgkin's disease is still unknown, nor does the nature of the condition appear to have been positively established. As has already been indicated, the earlier writers on the subject—granted the same condition was described which to-day we call Hodgkin's disease, *sensu stricto,*—leaned rather strongly to the view that the process was a *malignant neoplasm of a sarcomatous nature.* Even to-day, although the pendulum of opinion has swung strongly and generally toward emphasizing the *infectious character* of the disease, it seems apparent that the process has many of the earmarks of malignancy. This fact is considered in the nomenclature of many observers, i.e., malignant granuloma (Pappenheim, Naegeli, Benda and others).

The proponderance of evidence, however, points toward an infectious origin of the disease. This evidence is based primarily upon the histopathology of the affected tissues, and is partly of a positive and partly of a negative character. The positive element is the resemblance exhibited by the changes produced in the glands and other lymphatic tissues to those caused by the other known infectious granulomata, particularly tuberculosis and syphilis—a resemblance at times so close as to render a differential diagnosis a matter of the greatest difficulty. In a negative way, the infectious origin is emphasized by the total dissimilarity, on the whole, of the Hodgkin's tissue to that of the clinically similar leukemic and lymphosarcomatous lymph-node enlargements.

The matter of the temperature can hardly be adduced in favor of any of the etiological theories, as fever is observed both in the lymphosarcomata and in the leukemias, especially in their more active types; the temperature curves seen in Hodgkin's disease probably represent no more than secondary infection of the lymph-nodes, a complication which is known to be almost the rule. In brief, though we believe Hodgkin's disease to be an infectious granuloma, we shall be unable to state this definitely until the specific organism has been established according to the accepted rules of bacteriology.

The result of the enormous amount of research directed toward the discovery of the microörganism, or microörganisms, responsible for Hodgkin's disease has thus far yielded nothing of a positive character. The specific cause, if such there be, is still unknown.

A great many *organisms of various types* have at one time or another been regarded as the specific mycotic agents. As observed by Ziegler, the very multiplicity of organisms found in association with the disease speaks against the specificity of any one of them. With the exception of the tubercle bacillus and the pseudodiphtheria bacillus, to which special attention will be given, the writer believes that the numerous microörganisms—staphylococci, streptococci, pneumococci, *Bacillus coli*, *Bacillus subtilis* and other coccus and bacillus forms—and the isolated finding of spirochetæ and protozoön-like cell inclusions—which have been noted by different observers in the affected tissues or in the blood, or in both—are all to be looked upon either as accidental findings or as the agents of the secondary infections which are so frequently implanted upon the specific process.

The recent work of Bloomfield on the bacteriology of lymph-nodes which are apparently normal or obviously pathologic is especially instructive in this connection. The details of his studies will be discussed in connection with the relation of the pseudodiphtheria bacillus to Hodgkin's disease (see page 115).

As to the occasional finding of one of the above-mentioned bacteria in the blood stream, it seems likely to the writer that the secondary infection may just as well be responsible therefor as the assumed primary infection and, further, that the isolated finding of many bacteria in the blood stream may have little or no significance.

A further criticism directed against the different bacilli and cocci found at various times in association with the disease is that with none of them has an unequivocal instance of the condition been produced in experimental animals. Immunological studies have not furnished a basis for considering any particular organism employed in the study as specific.

The matter of the etiological relationship of the tubercle bacillus to the disease is still not definitely settled, although a majority of observers are of the opinion that Hodgkin's disease is due neither to the tubercle bacillus of the ordinary type nor to anomalous forms of the tubercle bacillus—granular, attenuated, etc.—nor to toxins of that organism.

Intensive investigation relative to the possible rôle of the *Bacillus tuberculosis* in the causation of the disease may be said to date from the publication, in 1898, by Sternberg, of a paper on "A Peculiar Form of Tuberculosis of the Lymphatic System Resembling Pseudoleukemia" (Ueber eine eigenartige, unter dem Bilde der Pseudoleukämie verlaufende, Tuberkulose des lymphatischen Apparates). The unusual histological picture of the affected lymph-nodes described by Sternberg differs in no way from that which we now know to be the histopathology of Hodgkin's disease. Later publications by the same observer confirmed his view that he had to do with an atypical form of tuberculosis of the lymph-nodes. For example, in 15 of his 18 cases, Sternberg states that he was able to establish a tuberculous etiology either by direct staining of the affected nodes or by animal inoculation. The assumption of such an etiology was in his opinion strengthened by the fact that in certain of his cases tuberculosis existed elsewhere in the body and that, in still other cases, typical tubercles were present in the same nodes, showing the peculiar granulomatous tissue.

To answer the arguments of Sternberg is not difficult, on the basis of our present-day conception of the nature of Hodgkin's disease. It is admitted that the finding in affected nodes of typical tuberculous changes side by side with the changes produced by the Hodgkin's process is not infrequent, that the coëxistence of Hodgkin's disease and tuberculosis elsewhere than in the lymph-nodes is not uncommon, and that animal inoculation experiments yield a certain number of positive results. Possibly in one-fifth of the cases the two processes are coëxistent, while in about one-tenth of the inoculation experiments tuberculosis is produced in the animals employed. In reply to the foregoing arguments the following facts seem evident:

1. The percentage of cases in which the conditions coëxist and in which animal experiment is positive is too small to prove anything more than that the tubercle bacillus is a secondary invader, finding in the tissues altered by Hodgkin's process a favorable soil, just as is the case with the other microörganisms which have already been mentioned in connection with the disease.
2. The mass of negative animal experiments far outweighs that of the positive (the work of Longcope, Simmons, Reed, Warnecke, Yamasaki among others).
3. The occasionally positive von Pirquet, Calmette and other tuberculin reactions mean no more than the occasional complicating tuberculosis.
4. The various phases of the Hodgkin's granulomatous tissue are, in the great majority of cases, quite unlike those of tuberculosis, and suggest a distinct etiology.

A new trend to work along these lines was given when Fraenkel and Much—and, in confirmation, many others—isolated from lymph-nodes showing the characteristic histological picture of infectious granuloma, a granular, Gram-positive, antiformin but not acid-fast rod, which, when injected into guinea pigs in the form of a glandular emulsion, produced typical tuberculous lesions containing the Gram-positive granules and rods. They called this organism, therefore, a granular form of the tubercle bacillus, and believed it to be responsible for the peculiar histological picture of Sternberg.

For the moment we shall dismiss the subject of the granular bacillus of Fraenkel and Much by stating that it is identical with the *pseudo-diphtheria bacillus* upon which attention has so recently been focused, and which we shall consider shortly. By way of digression we shall touch briefly upon another phase of the tuberculous question, i.e., that of the significance of the *bacillus of bovine tuberculosis.* This phase was revived a few years ago by Steiger who, on the basis of a comprehensive clinical and experimental study, came to the not entirely novel conclusion that Hodgkin's disease was due to the bacillus of bovine tuberculosis. He apparently demonstrated, among other things, that patients with the disease who showed no response to any of the human tuberculin tests did react positively to the von Pirquet and Calmette methods when material from the bovine organism was used; and by employing glandular emulsions assumed to contain this organism, he reported that he was able to reproduce the characteristic granulation tissue in rabbits.

Assuming the correctness of the opinion that Hodgkin's disease is not due to any of the several forms of the tubercle bacillus nor to one of the common mircoörganisms already mentioned, the writer believes that the most cogent argument against the theory that the bovine bacillus plays a rôle in this condition, consists in the fact that the tissue changes of the disease are too constant and fixed to admit of the assumption that they are caused by an organism which ordinarily produces histological changes of so different a character.

The intense interest recently aroused by the numerous studies devoted to the specific etiological significance of a *diphtheroid bacillus* in Hodgkin's disease has been almost entirely dissipated inasmuch as further work has demonstrated that this organism occupies a place of no more importance than the various other mycotic agents already mentioned in connection with the process. These others, in some instances, are unquestionably secondary invaders producing distinctive secondary changes, whereas the diphtheroid bacillus is probably nothing more than a saprophyte.

The history of the association with Hodgkin's disease of the pleomorphic, non-acid-fast, but antiformin-fast organism variously called a pseudodiphtheria or diphtheroid bacillus, the *Cornyebacterium granulomatis maligni* and even the *Bacterium hodgkini,* from the first description by Fraenkel and Much to the later ones of de Negri and Mieremet, Bunting and Yates, Billings and Rosenow, cannot be dismissed with a mere word because of the very recent widespread view that the specific cause of Hodgkin's disease has finally been discovered.

The opinion of Fraenkel and Much that this organism is an anomalous form of the tubercle bacillus has already been alluded to. In this particular they differed from the great majority of later observers. Of the latter, Bunting and Yates went furthest in emphasizing the specific etiological position of the organism in Hodgkin's disease. For a time, indeed, their work carried conviction, in view of the regularity of the occurrence of the organism in their cases, because of their ability to obtain it in pure culture from the affected tissues, and of their apparent success in transferring the disease in a characteristic form to the rhesus monkey. In addition, their findings, so far as the results of cultural experiments went, received ample confirmation.

Although this striking regularity of occurrence of the diphtheroid bacillus in Hodgkin's disease was at first naturally regarded as very strong proof of the specific etiological rôle of the organism, evidence soon accumulated which robbed this point of much of its apparent worth. In this category, the following considerations are especially valid:

1. A diphtheroid organism has repeatedly been recovered in conditions of quite a different nature from Hodgkin's disease. Thus, it has been isolated from the lymph-nodes of lymphoid leukemia, it has been found in lymphosarcoma, multiple neurofibromata, arthritis deformans, goiter chloroma, Banti's disease, and in many other conditions; and it is not infrequently present in lymph-nodes which are apparently normal. All of this indicates the accidental character of the bacillus.

2. The diphtheroid, as we have already noted, is only one of numerous organisms which have been cultured from the specific tissues of Hodgkin's disease.

3. Immunological reactions have failed to confirm the specificity of the organism. Observers have been able to obtain what appeared to be satisfactory antigens in their work, and yet in only a single case—one in which syphilis was also present—did they observe fixation of complement. In the process of active immunization with this organism, studies have not shown an increase in the specific agglutinative power of the patient's serum.

4. Most convincing were the results of a cultural study by Bloomfield, who, in a mixed series of cases, some with practically normal lymph-nodes, others with a distinct pathology, isolated twenty-nine different strains of organisms. More positive cultures were obtained from diseased than from relatively normal glands. No correlation was evident between a given organism and a specific tissue change. The relative avascularity of the lymphoglandular tissue possibly predisposes to the localization of microörganisms, some of which may be traced to contiguous infections, while others are saprophytic and correspond to the flora of the body surfaces. In Bloomfield's opinion, the diphtheroid

bacillus belongs to this latter class, which would account for its occasional presence in normal glands and its frequent or, as the case may be, regular occurrence in pathological tissues which favor its growth.

5. Finally, as to the conveyance of the disease to experimental animals, there is practically no evidence confirmatory of early positive reports. It is probable that in the animals which survived the inoculations the adenopathies were no more specific of Hodgkin's disease than were those produced by the injection of tissue emulsions containing the other organism found from time to time in the affected lymph-nodes of the disease.

As to the exciting cause of Hodgkin's disease, therefore, we come perforce to the conclusion that we are as far removed from a solution as before the bacteriological era. None of the organisms mentioned above stands up under the test. Yet there is no evidence against, and much in favor of the assumption that Hodgkin's disease is an entity, that it is an infectious granuloma, and that it is produced by a specific microörganism.

Mode of Conveyance.—The hypothetical organism responsible for Hodgkin's disease differs from the undiscovered organisms of other undoubted infections (measles, scarlatina, etc.) in that nothing is known of its mode of conveyance. This much can be said, however, that from the preponderating initial involvement of the cervical chain of lymph-nodes, one may surmise that the responsible bacterial agent, so far as its mode of entrance goes, favors the susceptible structures of the head, probably chiefly the mouth.

Symptomatology.—A BRIEF SURVEY OF THE CLINICAL PICTURE.—Trousseau's division of the clinical course of Hodgkin's disease into two phases, (*a*) that of the beginning, or local, enlargement of the lymph-nodes (latent period), and (*b*) that of the generalization of the process with the involvement of the lymph-glands generally, of the spleen in most cases and of other organs, and of progressive cachexia, is convenient for descriptive purposes, and aptly fits the majority of cases. That it is at best schematic, however, will appear later in connection with the discussion of the different types of the disease. (See page 138.) In this preliminary clinical survey, in which we shall consider primarily only what may be called the usual type of the condition, such a subdivision may be made use of to good purpose.

Latent Period.—The observant patient will tell the physician that the first evidence of something amiss was the appearance, on one side of the neck, of a growth, or tumor, which caused him no pain, was not tender and did not seem to affect his general health. The more intelligent individual is likely to present himself early with such a unilateral involvement of the cervical nodes. More frequently, however, the disease has made substantial progress before a great deal of attention is paid to it; it has gone on to the formation of a large mass on one side of the neck, with perhaps a few, small lymphomata on the opposite side

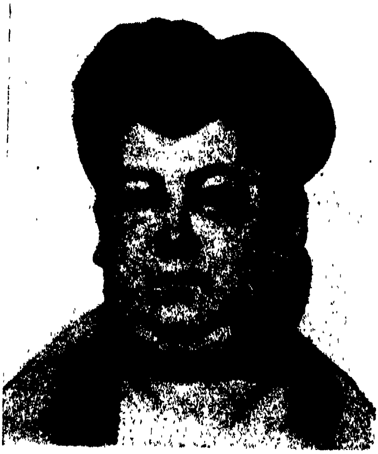

FIG. 1.

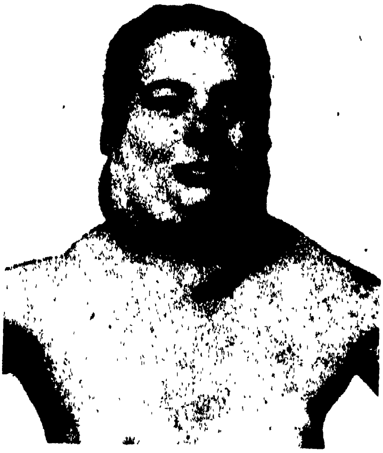

FIG. 2.

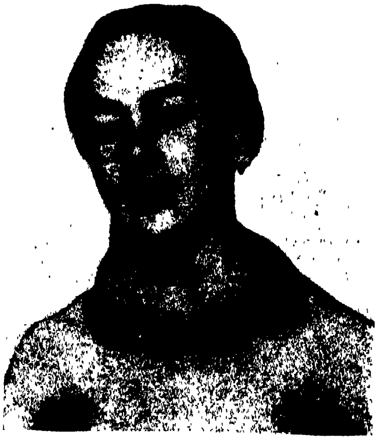

FIG. 3.

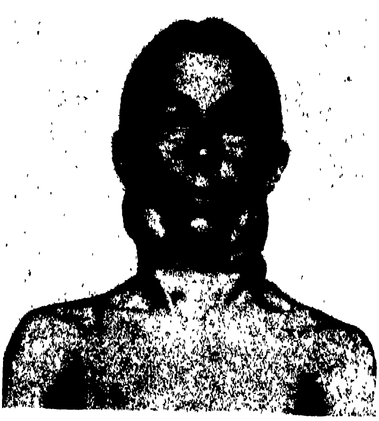

FIG. 4.

FIGS. 1-4.—HODGKIN'S DISEASE. Cervical tumors predominatingly left-sided (Fig. 1), right-sided (Fig. 2), bilateral in the lower half of the neck (Fig. 3) and in the upper half (Fig. 4). (From Kurt Ziegler, Die Hodgkinsche Krankheit, Jena, 1911.)

and often a node or two in one or both axillæ; or there are large tumors on both sides of the neck, apparently encircling the same (Hodgkin's collar, *See* Figs. 1 to 4) with smaller masses in other groups (axillæ, groin, etc.); or, in the more extreme cases, medical advice is not sought until the second phase is already well advanced. Instances of the latter, if not the rule, are at least extremely common in the larger public institutions.

A careful anamnesis will develop the fact, in a certain percentage of the cases, that the appearance of the cervical enlargements was preceded (for a period of variable length) by a pruritus, or by an exanthem of an itching character—manifestations of short duration, which may have appeared and disappeared several times. Cutaneous symptoms of this kind, the details of which will be taken up later, bear a variable time relationship to the disease proper. They may precede the beginning of the lymph-node enlargements for an indefinite period, never to reappear; they may subside with the onset of the adenopathy; they may begin early in the course and persist indefinitely; or they may not manifest themselves until after the nodes have begun to enlarge. In conjunction with the characteristic, slow, symptomless enlargement of the glands, these dermatoses may have a considerable diagnostic significance, especially if the history reveals that another premonitory manifestation, diarrhea, has been present.

The minority of cases which begin or run their early course in a manner different from that just described will be considered in detail under Clinical Types. (*See* page 138.) One finds:

1. Cases which have no distinct latent period, but exhibit a stormy onset with a succeeding rapid involvement of other nodes plus the ordinarily late general manifestations of the disease.
2. Cases in which there is more or less of a simultaneous hyperplasia of all lymph-glands.
3. Cases which begin with pressure symptoms, depending upon the initial involvement (dyspnea, jaundice, sciatica, abdominal pain, edemas, etc.).
4. Cases in which the superficial adenopathy appears late, being preceded by general symptoms of infection and toxemia, such as febrile manifestations, anemia, and loss of weight and strength (retroperitoneal initial involvement).

Instances of what we have called the common type, which come under observation during this early period, although subjectively symptomless, are likely at one time of examination or another to exhibit mild febrile phenomena and minor variations from the normal in their blood-picture, such as a slight leukopenia or slight leukocytosis and a relative increase in the mononuclear elements, both of the lymphocytic and large mononuclear types. A relative eosinophilia is also of frequent occurrence, and, when present, is of great diagnostic significance.

The duration of the so-called latent period—referring once more

FIG. 5.—HODGKIN'S DISEASE—GENERALIZED FORM. A case observed by the author with Dr. Charles A. Elliott. Photograph kindly loaned by Dr. Elliott.

only to the average clinical picture—is highly variable, depending, in part, probably upon the virulence of the infection, and, in part, upon the resistance of the individual. The literature gives variations of from several weeks to four years or more (seven to eighteen years). From a little less than a year to a little more than a year may be called the average duration. Other factors naturally enter into those cases in which pressure phenomena predominate in the early period.

Generalization Period.—The second period of Trousseau witnesses the generalization of the process, as far as the lymph-nodes are concerned, the involvement of other lymphatic structures, and of other organs, febrile phenomena and the appearance of anemia and cachexia. It seems to be the rule, perhaps, as marking the transition from the first to the second phases, for the process to show renewed activity in the group of nodes first involved; the glands of this group become larger, adjacent nodes appear and eventually, a massive, nodular tumor mass is formed. During this transformation, or, as the case may be, following it, other groups are affected—the cervical chain on the opposite side, the axillary, inguinal and other superficial groups (submaxillary, occipital, cubital, etc.) and, sooner or later, the deeper sets of glands. The spleen and liver undergo enlargement, and there may be signs of pressure phenomena exerted upon the lungs, pleuræ, hilus of the liver, nerve-trunks, veins. The mode of generalization of the lymph-node hyperplasia varies considerably; generally, after the renewal of activity in the group first involved, which ordinarily is the seat of the largest tumor mass, the progress to other groups is more or less orderly, but in some cases the involvement of new groups is a stormy and disorderly one, corresponding to no rule of lymphatic metastasis.

The other side of the picture of the second period is made up of manifestations due to the infection itself or to its toxins. *Fever* is present in the great majority of cases at some time during this stage; its type is variable, as we shall see elsewhere in this article. *Changes in the blood* are common but not invariable: many cases exhibit a neutrophilic leukocytosis of variable degree, others, a leukopenia, with a relative lymphocytosis. An eosinophilia is frequent and distinctive. In nearly all instances, an anemia of the secondary type develops. The grayish-yellow color of cachexia manifests itself, the patient gradually loses in strength and weight and is finally forced to his bed. Indeed, the picture of this later stage differs in no way from that of malignancy, as far as the constitutional manifestations are concerned.

We have already alluded to those special symptoms which in the later stages of the disease may be superimposed upon the usual form—pressure phenomena, depending upon the involvement of certain groups of nodes. (*See* Lymph-nodes, page 121.) There are several other forms of termination of the condition in addition to gradual exhaustion, with or without life-terminating pressure effects, namely, terminal septic infections involving the serous membranes and the lungs particularly, or the organs generally, and a terminal tuberculosis with its primary focus in the lungs or intestines and often with general miliary distribution.

The duration of the disease as a whole is highly variable, largely because of the variable length of the first stage. One to two years may be given as the average. In Ziegler's series not quite half of his patients lived longer than a year after the onset. Few live longer than four years after the onset; many succumb during the first six months. Treatment may bring about temporary halts in the progress of the condition, as may certain intercurrent infections, before the involvement has become too extensive, but the outcome is probably always death.

SYMPTOMATOLOGY IN DETAIL.—*Organs of Lymphatic Structure.*—The essential pathology of Hodgkin's disease is that of the changes in the lymphatic system. The involvement of the lymph-nodes and of the spleen is the most important in this connection.

(*a*) *Lymph-nodes.*—A brief account of the varying behaviors of the lymph-nodes has already been given. In the typical case—and this applies to half or more cases in most published series—a superficial group of glands is first affected (52 of Gowers' 78 collected cases and 71 of Longcope's 86 cases). Of the superficial groups, the cervical is by far the most frequent seat of the primary involvement. This, as had already been noted, is the classical beginning of Hodgkin's disease: a slow, painless enlargement of one of the cervical chains, generally of the posterior triangle. Opinion differs as to which group is next in frequency of involvement in the initial attack; this is of much less interest and importance than the fact that the cervical nodes are by far the ones most often affected primarily. The axillary, the inguinal, the submaxillary, and the occipital nodes are all at times the point of early localization of the process, while of those cases in which the deep glands are first involved, the mediastinal and retroperitoneal forms do not differ greatly in frequency.

Once the disease has established itself, the behavior of the group first involved and of the lymphoglandular system generally varies widely. Ordinarily, the primary group enlarges slowly, and without producing symptoms, both by the increase in size of the particular nodes first affected, by the involvement of other nodes of the same group, and by the formation of new nodes. The duration of this early tumor formation has already been discussed. (*See* page 120.) In other cases—but this is far less frequent—the primary process leads to the formation of only a small mass, after which another group is affected—the other cervical, or an axillary or still another group—and in this second set arises the large mass ordinarily observed in the chain first attacked.

There is no rule as to the method of spread, from group to group, of the infectious process. As a general thing, perhaps, the tendency is for the disease to advance from group to group in an orderly fashion in the direction of the lymph-current, thus forming a more or less continuous strand connecting the groups. However, the spread may be retrograde—against the lymph-current—as from the supraclavicular to the cervical or submaxillary. In other cases, the infection may leap from group to group without evidence of intermediate disturbance, e.g., from the cervical chain of one side to that of the other, or from the axillary group of one side to the inguinal of the other. However, in some of these cases with an anomalous spread, the autopsy reveals that some intermediate step existed in the involvement of the deeper groups of the neck, chest and abdomen.

The time element in the passage of the infection to the secondary groups of nodes also varies considerably in the different cases. Generally, the growth of the primary mass is slow, this representing the so-called latent period of the disease. With the renewal of activity, the original tumor increases in size both by the growth of nodes already involved and by the spread of the process to new glands, while simultaneously or shortly afterward, the generalization of the disease is signalized by the involvement of other sets of glands. In the acute cases, however, there is no more or less quiescent interval, and the process quickly spreads from group to group, giving the impression, almost, of a simultaneous general involvement. This type terminates very speedily in death either by cachexia or by the pressure effects of glands involved.

The diverse pressure effects of the growing glands will be considered in connection with the various organs involved.

As is the case with all other features of the lymph-node involvement, there is considerable variation in the characteristics and fate of the nodes of a particular group. In the first place, the individual glands differ greatly in size, ranging from that of a pea to that of an orange or fist, or larger. The particular group may be made of many nodes of the smaller type or of a variable number of small and large glands. Commonly, a given mass is found to be composed of one or several large or enormous nodes and, for the remainder, of a number of easily differentiable smaller units. Furthermore, while, in one case, all of the individual glands are well isolated from one another and freely movable, in others they form packets of closely adherent units which cannot be separated from each other. Secondary infection and the *x*-ray are especially likely to produce such conglomerates of matted gland. Only in exceptional cases do the masses become adherent to the overlying skin or undergo purulent degeneration, with or without sinus formation. As in the case of glands adherent to one another or to the skin, so when suppuration and sinus formation occur, secondary bacterial invaders are probably at work. A complicating tuberculosis may also possibly play a rôle.

The consistency of the glands is likewise variable. In the light of the histologic changes, the younger nodes should tend to be relatively soft and those longest involved, firm. Yet this is by no means always the case, as the early glands may be firm and those last affected soft and even semifluctuant, owing to secondary infection. The same nodes may be soft at certain times and firm and inelastic at others, depending possibly upon lymph-stasis and other circulatory factors. For the same reasons, the size of the individual nodes may vary from time to time.

An uncomplicated gland involvement is almost always painless. Pain, when present, is due either to secondary infection or to nerve pressure effects.

(*b*) *Spleen.*—The spleen is involved in the stage of generalization in perhaps three-quarters of the cases. In size, the organ is generally moderately large, although enormous tumors are occasionally observed, and it is usually firm in consistency. The surface is generally smooth. In a few cases the involvement of the spleen so far outweighs the other pathologic changes as to warrant a special nomenclature—the splenic type. (*See* page 140.)

(*c*) *Thymus.*—The thymus is occasionally involved in the process, with symptoms not differing essentially from those produced by an enlargement of the mediastinal glands.

(*d*) *Tonsils.*—Involvement of the tonsils is not common.

Organs Other Than Those of Lymphatic Structure.—Clinical phenomena exhibited by organs other than those of lymphatic structure are due in part to specific involvement of the same, in part to the effects of an infection, as such, partly to a cachexia-producing and an anemia-producing process, but chiefly to the pressure exerted by a growing mass of lymph-glands. As might be expected from the diversity of location of such masses, the various organs are quite differently affected in the different cases.

(*a*) *Circulatory System.*—Specific involvement of circulatory apparatus is not common. The infectious process and the anemia combine to produce a pulse that is generally rapid, small and of low tension, and the blood-pressure is usually low. Pressure phenomena are common. Displacement of the *heart* itself may be due either to a massing of the glands in the mediastinum or to a pleural collection of fluid, with a resulting sense of suffocation and dyspnea, and, at times, cardiac irregularity. Vagus phenomena (bradycardia or tachycardia) due to pressure are occasionally observed.

Phenomena due to compression of *blood-vessels* are, however, by far the most commonly observed clinical manifestations of involvement of the circulatory apparatus. In this respect, the *veins* are more readily affected than the arteries. The symptoms of venous compression are venous dilatation, and, in the case of the larger vessels, edema, of the parts supplied. Such venectasias involving cutaneous vessels are especially common on the thorax, particularly in the upper interspaces, about the axillæ, on the arms and on the neck. Compression of a large trunk, such as the axillary or the femoral, may produce not only dilatation of the visible veins of the extremity affected but also, as previously noted, a variable enlargement due to edema. Even the venæ cavæ may be compressed by the growing tumor masses with the characteristic circulatory phenomena. Pleural extravasations, usually unilateral, may be caused by pressure upon the intrathoracic veins.

The lymphatic circulation is also frequently affected by pressure, leading particularly to *edema of the chest wall* in the region of the sternum and mammary glands, and of the *neck and face* when a growing cervical mass is the cause. Attention has been called to the fact that periodic variations in the size of glandular tumors is probably due in the main to varying pressure upon lymphatic channels.

(*b*) *Respiratory System.*—Although the characteristic granulation tissue of the disease may involve the lungs by extension along the lymphatics from the hilus, manifesting itself chiefly in the form of a diffuse bronchitis, clinical phenomena on the part of the organs of respiration are chiefly due to pressure. The trachea may be compressed or displaced to a variable degree by cervical tumors, causing the characteristic stridor. Paralysis of a vocal cord may result from pressure upon a recurrent laryngeal nerve. The trachea may be involved also in its lower portion by a mediastinal process, as may also one of the main bronchi, evidencing itself chiefly by distant breathing, sometimes with unimpaired resonance on the affected side. An auscultatory change of this sort affecting an apex may cause difficulty in excluding tuberculosis as a cause. An advancing mediastinal mass, finally, may cause more or less pressure atelectasis of adjacent portions of pulmonary tissue, the clinical signs of which may offer considerable difficulty in interpretation.

Collections of fluid in one or both pleural cavities are not uncommon in this disease. They may be due to one or more of several causes. They may be the result, in the first place, of a specific (Hodgkin's) involvement of the pleural endothelium. In some cases, a complicating tuberculous pleuritis is the sole or contributing factor. Venous trunk compression, as already noted, accounts for the fluid in other instances. And, finally, the pleuritic factor may be part of a secondary infection so frequently observed in this condition. Chylous exudates have also been reported.

(*c*) *Digestive System.*—Of the organs comprising the digestive system, the liver most often participates in the process. The principal clinical manifestation observed in considerably over one-half of the cases is an enlargement of a variable degree which is dependent in part upon toxic factors and in part upon deposits of specific granulation tissue. The latter may exist in the form of miliary lymphomata or as tumors of considerable size. The liver surface is generally smooth, although at times nodular, because of the presence of these larger tumors. It is usually firm in consistency. *Jaundice* may follow compression of the common duct by the lymphomatous masses.

Diarrhea is a commonly observed symptom. Attention has already been called to its frequency as a so-called initial symptom, often in association with cutaneous lesions. It may be present, however, at any time during the course of the disease. Its cause is not clear and is possibly not the same in all cases, being in some a toxic manifestation, in others the indication of a specific involvement of the intestinal lymph-follicles. In the diarrheas of the later stages the possible etiological significance of tuberculosis and of a general secondary infection must be considered.

Dysphagia is occasionally observed and is due to compression of the esophagus by mediastinal masses.

The same etiological considerations discussed in connection with pleural exudates are applicable to *ascites* as a manifestation of peritoneal involvement.

(*d*) *Genito-urinary System.*—Clinical manifestations on the part of the genito-urinary tract are relatively infrequent, although any portion may be the seat of deposit of the specific granulation tissue. The *kidneys*, for example, may exhibit large lymphomata. Albuminuria is the most common symptom, due less to specific involvement of the renal parenchyma than to toxic and infectious factors.

(*e*) *Nervous System.*—The nervous system, including the organs of special sense, is very frequently involved in the process, most often in the way of pressure upon peripheral nerve-trunks. The symptoms of the latter are highly variable, depending upon the location of the tumor mass and the degree of compression exerted by it. Pain is common and is of diverse etiology, being due in some cases to direct nerve pressure (pain in the arm, from involvement of the brachial plexus, in the leg, from pressure upon the sciatic nerves, in the chest and abdomen, from pressure upon spinal nerves by tumors of the deeply situated glands), in others to granulomatous involvement of the spinal or cerebral dura; and in still others to involvement of the periosteum and bones.

Other nerve-trunk manifestations are various paresthesias. Pareses and paralyses are also observed (extremity, facial, vocal cord, the sympathetic). Epileptic attacks, spastic paraplegias, combined cord lesions, manifestations similar to those seen in pernicious anemia, and tabes-like complexes have likewise been described.

Pupillary inequalities due to sympathetic trunk compression have been mentioned. Eye-muscle paralyses may follow basal deposits of the granulomata. Involvement of the orbit produces symptoms not distinguishable from those due to other tumors in the same situation. The remaining organs of special sense are but rarely involved.

(*f*) *Osseous System.*—Some mention has already been made of the symptoms produced by the lesions of the disease when they affect the *periosteum* and *bones*. Nodules of variable size appear, or diffuse infiltrates, affecting the ribs, sternum, long bones, the base of the skull and the orbital regions, which are firm and inelastic, although at times semifluctuant, and generally painful. Pain is due for the most part to pressure upon adjacent nerve-filaments. Even the bone-marrow is occasionally invaded. In this way clinical complexes to some extent resembling chloroma (i.e., in its peri-orbital and frontal localization) and multiple myeloma are produced.

(*g*) *Cutaneous Manifestations.*—These constitute a very frequent and important part of the symptom-picture of Hodgkin's disease. They may be roughly divided into two forms, one of which is surely a specific process and the other in all probability also specific. The latter comprise the superficial, ephemeral lesions and are probably of toxic origin, the former the deep-seated, destructive changes made up of the characteristic granulation tissue of the disease.

Attention has already been called to *pruritus* as an important initial symptom of the disease (in 10 per cent. or more of the cases). This manifestation not infrequently precedes the development of the first gland mass, and, as has been said, when associated with diarrhea, is of considerable diagnostic importance. In some of the cases the itching tends to disappear with the growth of the lymphomata; in others it appears late in the course of the disease; while in still others, it persists throughout the clinical course.

The pruritus may be due to no apparent cutaneous change, but brings in its train scratch marks, and later, perhaps, pigmentation and a roughness and thickening of the skin; or it may be due to pin-head, to lentil-seed-sized, flesh-tinted or pale red papules belonging to the group disease known as prurigo. The late results of the latter do not differ from those following a simple pruritus. Among the less frequently observed superficial types is a diffuse eczematous condition which may be of an urticarial or an exfoliative character.

These lesions may be localized or diffuse, but the elective sites are the extensor surfaces of the extremities and the skin of the trunk. The apparent effect of operative treatment of the lymphomata on these lesions is interesting; in some cases the skin shows a tendency to clear up after extirpation of gland masses, while in others, operation seems to bring about the first outcropping, as the case may be, or a recurrence of the cutaneous lesion.

The deep persistent lesions represent deposits of the Hodgkin's tissue in the skin. They appear as skin tumors varying in size, often of light or dark brown color, firm, soft, or even fluctuating, and exhibit a well-marked tendency to break down with ulcer formation. Histologically, they are found to be composed of the characteristic granulation tissue.

Among other occasionally observed cutaneous manifestations are *pigmentation*, previously noted as a late result of the itching lesions, but frequently unassociated with pruritus and of unknown cause (although lesions of the adrenals have been adduced in explanation) and hemorrhages into the skin, in part, probably, of toxic origin and in part, an accompaniment of the anemia and cachexia.

The position of *mycosis fungoides* in the pathology of Hodgkin's disease will be considered elsewhere in this article.

(*h*) *General Manifestations.*—(1) *Fever.*—Of the general manifestations of the disease the most important is fever. An elevation of temperature is one of the most constant symptoms of the disease, few cases running their course without fever.

Three types of temperature curve have been noted in Hodgkin's disease. The first is a *moderate, irregular, continuous* course. Frequent observations may show that some fever is present daily; or there may be weeks or months of the irregular curve with afebrile periods of variable duration. Most observers believe this to be the commonest type of temperature in the disease and to be the curve most characteristic of the specific progress of the disease. The other two forms —the recurrent and the remittent—probably occur less frequently but are certainly more striking, and, in association with other symptoms, are highly distinctive of this disease.

The *remittent* type may begin gradually or with chills, and is characterized by periods of high, more or less continuous fever (with the usual diurnal variations) alternating with afebrile periods. The fever during the febrile phases may also be of the intermittent type. Febrile and afebrile periods are of variable duration.

The *intermittent* type is often associated with chills and sweats, suggesting malaria or pyemia. Fever of this character may last for days or weeks, or longer, and may be followed by fever-free intervals, or may go over into temperature of the other types described.

So small a proportion of the cases come under observation during the initial or latent phase—when such a subdivision is applicable to the particular case—that there exists little information as to the behavior of the temperature during that period. From the data available, however, it would seem that fever of moderate degree, following no definite curve and of irregular occurrence, may be present; but, in the average case, it does not assume a position of sufficient importance to invalidate the term applied to this early stage, i.e., latent.

The temperature curves regarded as more or less characteristic of the disease are exhibited rather in the more generalized period of the process, or at *any* point in those types which show no definite division into phases. Although there is no fever curve typical either of the stage of the disease or of any particular manifestation on the part of the growing lymph-nodes, or of any given form of the disease, to this extent, nevertheless, a rule may be formulated, namely, that a moderate, irregular, continuous fever is likely to be observed during a slow, orderly progress of the disease from lymph-group to lymph-group, while a higher, remittent or intermittent curve is apt to accompany a stormy generalization, or a rapid and considerable enlargement of one or more groups. This rule, however, is subject to many exceptions, such, for example, as the entire absence of fever at all times, remittent or intermittent fever even during a *gradual* generalization of the process, and an irregular, continuous curve both during periods of slow progression and when the lymphomata appear, or enlarge, by leaps and bounds.

Furthermore, it is true of the average case that temperature—whatever the type—is not present throughout its course; febrile periods of days, weeks or even months may alternate with afebrile periods of similar duration. The afebrile intervals need not be the clinical counterparts of quiescent pathological periods. It is more or less typical also of the variable character of the febrile manifestations of this disease that the different types of fever—continuous, recurrent, remittent—

may all be represented in the same case with no apparent variation in nature of the pathological progress.

From the foregoing it is obvious that attempts to correlate a given form of temperature curve with a particular phase of the pathological picture have met with only indifferent success. Yet, it seems almost natural to assume that the orderly and gradual generalization of the process should be accompanied by an irregular temperature, by analogy with other granulomatous conditions, for instance, tuberculosis of the lymph-nodes. On the other hand, the higher and more striking curves, the remittent—with the usual daily variations—and the recurrent, with intervals which are fever-free—either or both being often associated with chills and sweats—would, with equal facility, allow the assumption that they are the counterparts of a complication which very frequently supervenes, namely, secondary infection with pyogenic organisms. In this connection, analogy with tuberculosis is again distinctly relevant. This view gains support from the fact that, during the later and more active periods of the disease—especially when the nodes show a tendency to sudden and considerable enlargement—a high polynuclear leukocytosis is usually present, and marked polynuclear infiltration is observed in lymph-nodes excised at such a time. In addition, streptococci and other pyogenic organisms are not infrequently found in the glands and in the blood stream.

These assumptions, although very attractive both from the clinical and pathological points of view, cannot be regarded as anything more than hypotheses. Although fever is apparently an integral part of the clinical picture of every case, we cannot, at the present time, say more than that the irregular, continuous type would seem to express the growth of specific granulation tissue, while the more striking forms—the recurrent and remittent—suggest, both by analogy and by reason of associated findings, a complicating accident, such as a superimposed pyogenic process.

(2) *Blood.*—The hematological picture of Hodgkin's disease has always been a topic of interest and of animated discussion. We have already called attention to Virchow's important contribution to the differentiation of the generalized lymphomatous conditions in the separation of the leukemias (of the ordinary type) on the basis of a distinctive blood-picture. Attention has also been called to the desirability of using the term pseudoleukemia, if it is made use of at all, to designate only those lymphatic leukemias which exhibit typical leukemic changes in the lymphatic tissue but no increase, or only a moderate increase, of the number of white blood-corpuscles in the circulating blood (aleukemic leukemias). The author will take occasion elsewhere to point out the differential features of the latter, as distinguished from Hodgkin's disease, inasmuch as the two processes may, under certain conditions, bear a very striking clinical likeness.

We may anticipate what will be said here concerning the blood findings of Hodgkin's disease by stating that, despite the considerable study devoted to the matter, with the possible exception of an eosinophilia, which in itself is not constant, there exists nothing except the histopathology to distinguish this lymphomatosis *under all circumstances* from those others—the leukemias excepted—which may pursue a clinical course.

There is practically a unanimity of opinion as to the behavior of the erythrocytes and of the hemoglobin. The red blood-corpuscles are reduced in number, at one stage of the disease or another, in nearly all cases. As a general thing, this reduction is part of the picture of the second phase—that of generalization—and is a manifestation of the cachexia; but in a minority of cases a more or less pronounced diminution may accompany the phase of local glandular hyperplasia. In most cases, the red corpuscles number from two to four million per cubic millimeter, but occasionally the number may fall nearly to the million mark. In some cases these cells do not vary greatly from the normal throughout the course of the disease.

The hemoglobin is reduced proportionately to the erythrocytes; in other words, the anemia is always of the secondary type. Correlated to this fact is another, namely, that the changes in the red-cells, when they occur, are those characteristic of secondary anemia. The cells are pale, and, on an average, smaller than the normal in size; and nucleated cells, if present, are predominatingly normoblasts. Poikilocytosis, polychromatophilia, and basophilic granulations may be seen in the severer cases.

There is considerably less agreement as to the behavior of the leukocytes. The total number is subject to marked variations. Ziegler, for example, found the following figures in 70 cases: in 22, counts of from 5,500 to 10,000; in 20, from 10,000 to 20,000; in 8, from 20,000 to 30,000; in 2, more than 30,000; and in 18, a leukopenia of from 2,000 to 5,500. But counts exceeding this maximum are by no means infrequent. (The author reported a case exhibiting 41,000 leukocytes per cubic millimeter on several examinations; and even higher totals are on record.)

In a very general way it may be said that in the early phases of the disease the total white-cell count is likely to be about normal, possibly slightly below, possibly slightly above, whereas, with the generalization of the disease, particularly if it is rapid or accompanied by the intermittent or recurrent type of fever course, a leukocytosis is common. This has already been commented on as possible evidence of the part played by secondary pyogenic infections in the later phases of the disease. Despite the above-stated average behavior of the leukocytes, it must be emphasized that the total counts may vary from the rule, irrespective of the stage of the disease, of the course of the temperature, and of the degree of the anemia.

A similar situation exists with regard to the different type of white blood-corpuscles. As in the case of the total number of leukocytes, a general rule may be stated: Early in the disease, with a localized gland mass, little or no fever and apparent good health, the lymphocytes are likely to be both relatively and absolutely increased, and the large mononuclear and transitional cells may show a similar tendency, with the generalization of the disease and especially during periods of marked febrile reaction, the lymphocytes are apt to be relatively diminished and the polynuclear neutrophils enormously increased. As this latter condition usually coincides with an increase of the total number of white-cells, the picture is that of an ordinary polynuclear leukocytosis.

The exceptions to this more or less usual picture are many. In some cases, for example, both the total white-cell-count and the differential count may be practically normal throughout the course of the disease. This is particularly apt to be the case in those forms which tend to remain localized—the cervical group, the mediastinal and retroperitoneal groups, and spleen. In the same localized types, a leukopenia may be present throughout—a condition fairly common in the retroperitoneal (typhoidal) form. Again, with a total count not far from normal, the polynuclear leukocytes may be relatively increased; this is more apt to accompany the later phases of the disease than the earlier, being due in part perhaps to the encroachment upon the lymphatic structures of the specific granulation tissue.

A leukopenia with a relative lymphocytosis may be present in some instances in the beginning of the disease, in cases of involvement of the deep nodes, and also in cases in which there seems to be a toxic overwhelming the bone-marrow—as is observed, for example, in typhoid fever.

The behavior of two groups of cells in particular—the eosinophils and the large mononuclears—has been looked upon by many as especially characteristic of the disease. This has been well substantiated in the case of the eosinophils. In the majority of cases they are relatively increased, even up to 25 per cent. or more of the total number. Although this increase is particularly apt to be present when the total count is about normal, it may be observed even when a marked leukocytosis prevails. However, this is certainly exceptional, for, as a rule, the eosinophils are markedly diminished or even absent during the periods of high leukocytosis, which accords with the well-known fact that in most acute infections the acidophilic cells tend to disappear from the circulation, reappearing with the beginning of convalescence. This is, in all probability, the case in Hodgkin's disease when a leukocytosis, high temperature, etc. (superimposed pyogenic infection) supervene.

A blood eosinophilia usually runs parallel with a tissue eosinophilia. It is probable that chemotactic influences exerted by the specific granulation tissue upon the bone-marrow bring in response not only the number demanded by the tissues but, as is usual, an excess, which enters the circulating blood. Thus the blood eosinophilia ranks in importance, as a diagnostic finding, with its tissue counterpart, and it is an almost invariable rule that in that minority of cases in which the acidophilic cell is absent in the specific granulation tissue, it is likewise absent in the blood.

An eosinophilia, therefore, is a manifestation of real diagnostic worth. When present, it is of distinct value in excluding those other general lymphomatous processes with which Hodgkin's disease may be confused. Lymphosarcoma, lymphatic leukemia, tuberculosis, and the other lymphomatoses do not often exhibit this symptom. An eosinophilia is especially significant if it is observed during one of those periods characterized by the phenomena of acute infection (high fever, leukocytosis, etc.).

An increase in the large mononuclear and transitional cells has also been regarded by some as especially characteristic of the disease, particularly in its early phases. It is true that such an increase (from 5 to 20 per cent.) is not infrequently the case, but the finding loses in diagnostic significance because it occurs in a number of other conditions in which there are lymph-node changes with a destructive tendency (tuberculosis, metastatic carcinoma of the nodes, etc.).

In résumé, it may be said, that, despite the variability of the blood changes in Hodgkin's disease, many cases tend to show what may be termed an average picture, both as regards the grade of the anemia and the total and relative counts of the white blood-corpuscles. In addition, the frequency of an eosinophilia in this condition as contrasted with those other processes likely to cause confusion, is of real diagnostic value.

Diagnosis.—The final, and in some cases the only, diagnostic criterion is the microscopical examination of the excised lymph-node. However, in this section on Diagnosis we are particularly interested in those features of the clinical picture which seem to warrant a diagnosis of the disease before the microscope is used. The more usual forms of Hodgkin's disease are, as a rule, after proper study and sufficient observation, not difficult of diagnosis on the basis of the clinical course alone. The less common types offer greater, and sometimes insurmountable, obstacles to recognition. The splenic form, the types beginning in or predominantly involving the deeper nodes (retroperitoneal, mediastinal) will be more often recognized as these less frequent clinical forms become better known and are given proper weight in the differential diagnosis; yet, even with this proviso, in many cases, it is only on the basis of the behavior of the superficial nodes, and by microscopical examination of the same, that a definite conclusion can be reached. These points will be more fully considered in the section devoted to Differential Diagnosis.

In the average case, frequently referred to in the preceding pages, the following points indicate that a given lymphomatous condition is probably to be diagnosed as Hodgkin's disease:

1. Premonitory symptoms of pruritus—with or without provocative cutaneous lesions—and diarrhea.

2. In those cases which are seen early, the slow symptomless development of a lymph-node mass in one of the several chains, usually cervical. The mass is not tender and gives rise to no spontaneous pain; the individual nodes are generally well isolated and are not adherent to the superjacent skin. The nodes are usually firm, but even if soft or apparently fluctuant, they do not break down, nor do they form sinuses opening externally. Important, also, is the tendency of the individual nodes to vary, from time to time, both in size and in consistency.

3. In those cases coming under observation late (after generalization has begun), the history of the above-mentioned initial period plus the further development of the glandular process, namely a more or less orderly involvement of group after group, the development, simultaneously, of an enlargement of the spleen and liver, and a progressive cachexia.

4. The presence of fever. Although not a distinctive manifestation, even if of the irregular, continuous type, this tends to render less probable the existence of other gland processes such as chronic lymphatic leukemia, lymphosarcomatosis, syphilis, metastatic carcinoma and other conditions. The less frequent forms, the recurrent and the remittent, in conjunction with the rest of the symptom picture, are highly suggestive of Hodgkin's disease.

5. The distinctive changes in the blood, for instance, the fairly constant eosinophilia, which is especially suggestive if associated with a well-marked leukocytosis. Another change consists in the high degrees of polynuclear leukocytosis. An increase in the large mononuclears, although common, is by no means pathognomonic.

6. Cutaneous manifestations—pruritus, prurigo, eczema—during the course of the disease.

The several subtypes of the disease depend for their recognition, first, upon the accompanying symptoms of localization (mediastinal, retroperitoneal, splenic, osteoperiosteal), secondly, upon the symptoms of the process as a whole (cutaneous manifestations, diarrhea, fever, cachexia, splenic tumor), and thirdly—and this is often the only distinguishing mark—upon the clinical behavior and microscopical picture of the peripheral lymph-nodes. The retroperitoneal (typhoidal) form is perhaps the most likely of all the less common subtypes to present features which suggest a correct diagnosis without the help furnished by lymphatic involvement elsewhere. The author refers to the frequent diarrhea, early skin manifestations, long-continued irregular fever, leukopenia, splenic enlargement, and negative Widal reaction and blood culture, yet he recalls 2 cases in which additional assistance was necessary for confirmation—in one, the autopsy, and in the other the appearance of cervical and axillary nodes, which on microscopical section showed the characteristic granulation tissue.

We may summarize our diagnostic limitations and possibilities as follows: A thorough knowledge of the onset and clinical course of the disease, plus an appreciation of the various clinical forms is, in the majority of cases, perhaps, sufficient to warrant a presumptive diagnosis of Hodgkin's disease. A positive diagnosis can rest only upon the histological examination of an excised node.

DIFFERENTIAL DIAGNOSIS.—This phase of the study comprises, first, the elimination of those various conditions—granulomatous, leukemic and malignant—which exhibit local or generalized lymphadenopathies with splenic tumor, progressive anemia and cachexia, and which together form that large group of lymphomatoses from which Hodgkin's disease has finally been separated; secondly, those diseases which simulate the various specially localized forms of Hodgkin's disease—splenic, typhoidal, mediastinal, osteoperiosteal, etc.—and, thirdly, a few other conditions which may be suggested particularly by the recurrent or remittent febrile types—endocarditis, malaria, etc.

Tuberculosis of the Lymphatic Glands.—This condition is probably the one most frequently to be distinguished from Hodgkin's disease in the differential diagnosis. In the majority of cases, perhaps, even on the basis of the clinical picture alone, the differentiation encounters no great difficulties, while in the remainder the distinction can be made only by the study of the histologic changes. Indeed, it occasionally happens that even the microscopical examination of an excised node is not decisive. The early lymphoid infiltration of Hodgkin's disease with little or none of the more characteristic cellular content may not differ materially from the lymphoid hyperplasia of a tuberculous gland before the formation of the diagnostic tubercles.

We may enumerate the more distinctive findings of the two conditions, laying emphasis upon those which indicate the one or the other.

1. The frequently observed prodromal manifestations of Hodgkin's disease—pruritus and diarrhea—are regularly absent in tuberculosis.
2. The presence of tuberculous changes elsewhere—in the lungs, bones, etc.—although not positive proof that the particular lymphomata are tuberculous, does testify in favor of tuberculosis and against Hodgkin's disease.
3. The more generalized forms of lymph-gland tuberculosis resembling the Hodgkin's picture are far more common in infants and children than in adults. This age incidence, in a general way, is evidence against malignant granuloma.
4. The constituents of the particular tuberculous lymph-node group tend to become matted together (periadenitis), and to become adherent to the skin; and softening and sinus formations are almost the rule.
5. As a general thing the tuberculous glands and gland groups do not reach the enormous size nor the extensive generalization of those of Hodgkin's disease.
6. The more characteristic temperature curves of Hodgkin's disease—the recurrent and the remittent—are rarely, if ever, observed in tuberculosis lymphadenitis, although very similar febrile manifestations may be present when a tuberculous glandular process is associ-

ated with extensive tuberculous changes in other organs, being evidence, in that case, of secondary pyogenic infection.

7. Certain phenomena of the blood may point toward one condition or the other. An eosinophilia, especially if present during periods of high fever and in association with a well-marked leukocytosis, is highly suggestive of Hodgkin's disease. In the case of localized lymph-gland tumors, especially of the cervical region, and more particularly in adults, a relative and absolute lymphocytosis points toward tuberculosis. High degrees of leukocytosis are far more common in the Hodgkin's than in the tuberculous granuloma.

8. The gland masses of tuberculosis rarely tend to vary greatly in size from time to time as do those of Hodgkin's disease (lymph-edema); nor is edema (from the same cause) of the face, neck and chest wall a frequent manifestation of tuberculosis.

9. The various forms of tuberculosis cutis and of the tuberculids are totally unlike the cutaneous manifestations of Hodgkin's disease already described.

10. It is not unlikely that some of the cases of so-called generalized lymph-node tuberculosis which run a clinical course indistinguishable from that of Hodgkin's disease, are really combinations of the two diseases.

11. Microscopically, the cut glands of tuberculosis are characterized particularly by the areas of caseation and softening, while in Hodgkin's disease, although small necroses may often be detected, extensive pus-like softening is due only to a tuberculous or pyogenic superimposed infection.

12. The microscopical picture of the two diseases is the definitive test. In the great majority of cases we observe on the one side the unmistakable tubercle—the details of which need not be entered into at this time—and on the other the characteristic granulation tissue of Hodgkin's disease which is described elsewhere in this article. Two exceptions to this clear-cut differentiation must be noted: first, those early cases of the two conditions, already noted, in which a lymphocytic infiltration is the prevailing change, and in which later examination may be necessary, and, secondly, mixed cases of the two diseases which can usually be interpreted by careful study.

Syphilis.—The other common granulomatous condition, syphilis, ordinarily causes no confusion in the diagnosis. As with tuberculosis, one must bear in mind that Hodgkin's disease and lues may coëxist in the same patient, in which case a somewhat more difficult problem is presented, and one in which only the histological picture of an excised node will be decisive.

The general adenopathy of the so-called second stage of syphilis—unless complicated by lymphomata of considerable size in one chain or another (tuberculosis, simple hyperplasias, etc.)—scarcely need enter into a differential diagnosis, because the luetic gland enlargements of this period are small, shotty, and relatively few in number, rarely forming packets of any size.

Somewhat similar considerations apply to the luetic adenopathies of the tertiary stage. Although lymphomatous masses of considerable size in one or more chains may appear, they rarely attain the proportions of the Hodgkin's packets, nor do they become so generalized. Luetic lesions elsewhere and the results of the Wassermann reaction, are also of determining importance. And, finally, in doubtful cases, the decision must rest upon the tissue changes observed in an excised node—those of syphilis resembling tuberculosis (absence of the pathognomonic enormous epitheloid cells, absence of tissue eosinophilia, giant-cells of the Langhans' type, etc.) more than Hodgkin's disease.

Non-specific Lymph-gland Enlargement.—In this place one may properly note that form of non-specific lymph-gland enlargement involving, as a rule, only the cervical nodes of one side, and at times causing temporary confusion with a similar localization in Hodgkin's disease (local stage). The writer has seen a number of these cases, in each of which a primary source of mischief has been found in the head (teeth, tonsils, accessory sinuses, etc.). The nodes of such lymphomatous masses are at first firm and discrete; and at all times they are tender. Later, they enlarge, become matted together and adherent to the skin, and finally may break down. The blood-picture is that of an ordinary polynuclear leukocytosis with none of the distinguishing marks of malignant granuloma; histologically, a lymphoid hyperplasia is found with a variable degree of polynuclear infiltration. Removal of the offending focus, or foci, generally results in complete recovery.

Leukemia.—The several leukemias may, in one case or another, require diagnostic elimination, but this is usually not difficult. Of all forms, the *chronic lymphatic leukemias* are most likely to cause confusion, and this is particularly true in the case of the so-called generalized form of Hodgkin's disease (*q.v.*). In contrast to the average case of the latter, which starts in a single group of nodes, and exhibits a variable latent period during this localization, followed by an orderly involvement of the other lymphatic groups, chronic lymphatic leukemia begins with universal enlargement of the nodes. Although the two conditions have many features in common, they are readily distinguished on the basis of the blood-picture of leukemia—an enormous increase in the white blood-corpuscles with an overwhelming relative lymphocytosis—and, if need be, by the histologic changes in the respective nodes, that of lymphatic leukemia showing *at all times* a simple lymphatic hyperplasia.

The writer has on several occasions alluded to the diagnostic confusion caused by those lymphatic leukemias which pursue their course with little, if any, increase in the total number of white cells in the circulating blood (*aleukemic leukemias*). Clinically, aside from the blood-picture, they differ in no particular from the more usual type of this leukemia. In the majority of cases a differentiation from Hodgkin's disease is readily made, inasmuch as the aleukemic leukemias present the same high relative lymphocytosis as do the ordinary forms. Final differentiation may be made on the basis of the histological picture, that of aleukemic leukemia being the same—simple lymphoid hyperplasia—as that of the ordinary lymphoid leukemia.

Chronic myeloid leukemia is only rarely a source of confusion, and then it must be distinguished from that form of Hodgkin's disease in which a splenic tumor is the outstanding symptom. The initial symptoms of pruritus and diarrhea, the febrile manifestations, the behavior of the superficial groups of nodes in the latter, and the typical myeloid blood-picture of the former, scarcely allow a doubt, even after a perfunctory study. Furthermore, the spleen of Hodgkin's disease, even in the splenic form, rarely attains the size of that of myeloid leukemia, and the histological picture of the latter—myeloid infiltration of the affected tissues—is a final diagnostic difference.

The *acute leukemias* may under certain conditions bear a resemblance to Hodgkin's disease, especially to the acute form of the latter, and to the type showing periosteal nodules. Aside from the typical blood-picture of the acute leukemias in which, even though at times the total number of white corpuscles may not be greatly increased, there is a great predominance of lymphoid—or, as the case may be, myeloid cells, usually of the large, nongranular form—there are other manifestations which lead the diagnosis in the right direction. These manifestations consist in the marked tendency to ulceration, often gangrenous, of the mucous surfaces, particularly those of the mouth, to high degrees of anemias, often greatly resembling the pernicious form, and to the hemorrhagic diathesis in the acute leukemias. In Hodgkin's disease there is not infrequently a history of a latent period preceding the acute generalization, of prodromal itching or other cutaneous changes and of the recurrent or remittent types of fever. Histologically, in acute leukemia there appears to be an infiltration of the affected tissues by the same type of large cells as are seen in the blood, while the epitheloid, giant-cell and eosinophil components of the Hodgkin's tissue are absent. As in all the leukemias, the tissue growth is likely to be infiltrative in character as contrasted with the more nodular metastases of Hodgkin's disease.

Chloroma.—Mention has been made of the resemblance borne by cases of Hodgkin's disease of the periosteal type, with especial periorbital and frontal localization, to chloroma, in the typical instances of which there is a similar involvement. The writer has no intention of entering into the discussion as to whether all or most cases of chloroma are in reality acute leukemias, lymphoid or myeloid. In those cases in which there is a hematological picture of an acute leukemia, the diagnosis is then and there established, while in other cases, the examination of an excised lymph-node must be relied upon to verify the diagnosis of Hodgkin's disease.

Multiple Myeloma.—Similar considerations apply to the condition known as multiple myeloma which clinically resembles the medullary type of Hodgkin's disease. Those forms, if any, belonging to the leukemias may be recognized by the blood-picture, whereas those of apparently other nature (neoplasmatic, inflammatory) must be distinguished from Hodgkin's disease by the absence of the more characteristic earmarks of the latter (superficial node groups, spleen, more characteristic fever curves, prodromata, etc.).

Metastatic Bone Tumors.—Metastatic bone tumors emanating from a malignant source (breast, prostate, suprarenals—hypernephroma) differ from tumors of similar localization in Hodgkin's disease by the presence in some of the primary tumor, by the frequently suggestive blood-picture of the former (an enormous number of nucleated red-cells), and by the absence of the diagnostic features of malignant granuloma.

Primary lymph-node malignancy (*lymphosarcoma*) may apparently pursue one of several courses: either that of an early localized lymph-node group involvement with subsequent metastasis (lymphosarcoma), or a generalized lymphatic condition (lymphosarcomatosis). In either case, the resemblance to corresponding forms of Hodgkin's disease may be very great. Further confusion is injected into the subject by the fact that many observers have believed, and still do believe, that Hodgkin's disease is a true malignancy of a sarcomatous nature. However, from the writer's point of view, the two conditions can often be distinguished as follows: first, by the clinical course of Hodgkin's disease (prodromata, febrile course, behavior of the individual nodes, etc.), secondly, by the behavior of the sarcomatous tumors (tendency to become matted together and to become adherent to the skin, hardness), and, thirdly, by the histological picture of lymphosarcoma which is that of an atypical—and monotonous—growth of the lymphoid constituents of the nodes as contrasted with the variegated cell-complex of the Hodgkin's tissue. Often, also, there is associated with lymphosarcoma, primarily or secondarily, a non-stenosing involvement of the gastro-intestinal tract.

Splenomegaly.—Those cases of Hodgkin's disease with considerable and, more particularly, with preponderating involvement of the spleen, require differentiation from the various splenomegalies. Some of them—leukemia, syphilis, tuberculosis—have already been commented upon. Applicable to all of the non-Hodgkin's splenomegalies are the following facts: Either there is no associated lymphadenopathy, or, if the latter is present, section of an excised node reveals the particular pathology as being not characteristic of malignant granuloma. In addition, the following distinctive points may be mentioned: in *malaria,* the history, the finding in the blood, in some cases, of the plasmodium (possibly after provocative use of quinin in the more chronic cases), the great firmness of the spleen, in *Banti's disease,* particularly the absence of lymph-node enlargements, the development of the ascitic stage and, anatomically, characteristic changes in the spleen, in *hemolytic icterus,* the frequent familial occurrence, the acholuric jaundice and the fragility of the red corpuscles, in *Gaucher's disease,* the familial history, the peculiar grayish-yellow or brownish color of the skin, the exquisitely chronic course and the histological picture, characterized particularly by the strands and groups of large, epithelial or endothelial cells, with relatively small nuclei, in the spleen, liver, lymph-nodes and other organs, and a diffuse hemochromatosis, and in *von Jaksch's anemia* (anemia pseudoleukæmica infantum) the characteristic blood-picture (secondary anemia, megaloblasts and normoblasts, myelocytes, etc.).

Typhoid Fever.—Typhoid fever enters into the differential diagnosis because of the clinical course of the so-called typhoidal form of Hodgkin's disease, already noted. The absence of changes in the accessible nodes, the presence of a positive Widal reaction, and the finding of typhoid bacilli in the blood stream are the points which eventually determine the diagnosis.

Pyemia.—Pyemia, including *ulcerative endocarditis, septicopyemia, malaria* (in its active stages), certain forms of gall-bladder and renal infection, may have to be considered in the differential diagnosis because of the temperature curves common to these conditions and to Hodgkin's disease. A thorough analysis of these various processes based upon points already sufficiently emphasized will generally permit of a correct interpretation of the particular case.

Clinical Types.*—Some of the more important of these subtypes have already been touched upon. The division into clinical forms is not a sharp one, as the different types tend to overlap and eventually, in most cases, to fall into a common mold. The onset, the early or chief localization, and the course of the disease are the factors determining the clinical subdivision.

LOCALIZED TYPE.—The localized type has been given considerable attention in the preceding pages. In this form, the disease begins with the gradual enlargement of a single group of nodes, usually one of those in the region of the neck. Here the process may remain quite localized for months, or even several years, producing few, if any, symptoms of a general nature. Depending upon its location and size, this primary mass may occasion variable pressure effects, as already noted. It is to this localized type, particularly, that the term *latent period* is especially applicable.

Sooner or later, latency goes over into renewed activity, the nodes of the primary group enlarge, new nodes appear in the same group, and generalization takes place by an orderly involvement of other chains or more or less simultaneously.

Strictly speaking the term *localized* is rather arbitrary, for it is probable that those forms which become generalized early also exhibit a brief, even though unrecognized, local stage; and other forms, dignified by special names, are equally of local character (the mediastinal, the retroperitoneal, the splenic).

The practically symptomless character of this early gland mass has been sufficiently emphasized, and the clinical features of the period of generalization have also been described in full in their appropriate places.

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* The classification of K. Ziegler has been used in this section.

GENERALIZED TYPE.—In the generalized form, with or without the usual premonitory symptoms, there arises a more or less universal enlargement of the various lymph-node groups, all within a relatively brief period. The process involves both the superficial and deep nodes, those of the neck, as in other types, forming the predominant masses. Involvement of the spleen and of the other organs is not long delayed and cachexia soon supervenes. The febrile reactions and the blood-picture are as already described. With evidences of progressive anemia and cachexia, death occurs either from general exhaustion and cardiac weakness or as a result of an intercurrent infection.

We emphasize once more the fact that the generalized form differs from the localized in a manner more apparent than real; in the former the development of the initial gland mass either passes unobserved, or is of relatively brief duration, while in the latter its slow development forms a well-demarcated initial period.

MEDIASTINAL TUMOR.—Localization in an area especially prone to the production of pressure symptoms is a chief characteristic of that type running the course of a mediastinal tumor. The beginnings of the process in this region may be centered either in the mediastinal group or nodes or, in all likelihood in some cases, in the thymus. The later development of the disease is variable; the primary mediastinal mass may grow to an enormous size, dominating the clinical picture by reason of compression phenomena with subsequently more or less involvement of the other lymph-node groups; or the mediastinal tumor may represent only the beginnings of the process, in itself attaining no great size, but followed by one or more enormous packets of glands elsewhere (for example, cervical) with a more moderate generalization in the remaining chains of nodes. The primary nature of the mediastinal localization may be revealed by pressure phenomena—pain, dyspnea, vessel or nerve compression—or it may be recognized, or perhaps only surmised, by the postmortem examination. It is not admitted by all observers, indeed, that a mediastinal Hodgkin's disease is ever primary, the contention being that one of the neighboring sets of nodes—cervical, peribronchial, or others—is originally affected, even though not in a striking fashion.

The symptoms of mediastinal tumor do not differ from those based upon tumors of other origin. Depending upon the size and direction of growth of the granulomatous mass, there is dullness over the upper sternum, with variable extension to the right or left. The area of impaired resonance resembles that of neoplasm rather than aneurysm, in that its borders are irregular, jagged, *not vascular*. There may be impaired resonance, or even flatness, in the intra-clavicular regions due partly to the granulomatous mass, itself, and partly to pressure atelectasis. Pressure upon a bronchus may cause apical dullness suggesting a tuberculous change, while impaired resonance may extend for a variable distance to the right of the sternum along its entire extent.

The roentgenological examination of such a condition confirms the irregular outlines obtained by percussion, and further eliminates aneurysm by revealing the absence of a pulsation in the mass.

The chief compression phenomena of such a tumor have been considered in connection with the discussion of the lymph-nodes. (*See* page 121.) In one case or another there may be signs of pressure upon the veins (intercostal, azygos, innominate, venæ cavæ), often with an associated edema of the sternal or mammary regions and of the arms, upon the nervus sympatheticus, upon the nervus recurrens, upon the trachea or bronchi, and upon the vagus. Pleural transudates are frequent.

According to Ziegler, this type tends to run a course like that of the so-called localized form: cachexia and anemia are late, if present at all; fever may be absent, and the general nutrition is often not affected. Death is likely to occur before generalization takes place, due to compression phenomena. He contrasts the true mediastinal type with that variety which involves the mediastinal lymphatic tissues secondarily; in the latter, further generalization proceeds apace, cachexia, fever and other symptoms of the second stage, are prominent, and the patient succumbs to exhaustion.

TYPHOIDAL TYPE.—One of the best demarcated types of Hodgkin's disease is that which for a time at least resembles typhoid fever (*typhoidal form*). The process is confined for a variable period almost exclusively to the retroperitoneal glands, the involvement of the superficial nodes at first being slight or absent. The onset is gradual, often with pruritus and diarrhea. Fever—sometimes continuous and irregular, at other times remittent or recurrent—loss of weight and strength, anemia, in some cases abdominal pain, go to make up the clinical picture. Later the spleen and liver enlarge. In some cases a positive diazo-reaction has been recorded. In general, with little involvement of the superficial nodes, the resemblance to typhoid fever may be striking, especially if a leukopenia is also present, as is often observed. Some cases have gone to autopsy before their true nature was recognized; in others the behavior of the peripheral nodes has served to clear up the situation, while in still others, the persistently negative blood-cultures and Widal reactions have suggested the possibility of Hodgkin's disease.

SPLENIC TYPE.—Occasionally one observes a disproportionate involvement of the spleen and lymph-nodes. The spleen may reach enormous proportions, and the superficial nodes may be only slightly affected. In other cases, an unusually large spleen seems to be associated with early involvement of the retroperitoneal glands. This dominance of the clinical picture by a splenomegaly suggests a primary localization in that organ and has given rise to the special form of the disease known as the splenic type.

The spleen may attain a size only secondary to that of myeloid leukemia. Its surface may be smooth or nodular. Leukemia is generally the provisional diagnosis, and can be eliminated in some cases only by the examination of the blood. In other instances, the behavior of the lymph-nodes, particularly the marked enlargement of a single group (cervical, retroperitoneal or others) suggests the correct diagnosis. The general symptoms of the splenic form—pruritus, diarrhea, fever, anemia, cachexia—do not differ from those of types already considered, and are of additional help in determining the true situation.

TYPE SHOWING SPECIAL LOCALIZATION IN BONE.—The resemblance of the type showing special localization in bone has already been noted. The outstanding features of this form are the nodular thickening of certain bones, deposits of the specific granulation tissue in the medulla of the bones and, in many cases, the association of extreme pain. The ribs and the sternum are sites of predilection for the periosteal lymphomata, although any bone may be affected. In some cases, large masses arise about the orbital regions and over the frontal bones, thus superficially resembling the characteristic chloromas. The pain in these cases is due both to direct pressure upon nerves and to actual bone compression.

Involvement of the medullary cavities, also, is not infrequent. Pain and localized enlargement of the bones call attention to the condition. The clinical resemblance to multiple myeloma may be very close; in fact, a differential diagnosis may be impossible unless simultaneous involvement of lymph-node groups is present.

The type involving bones is probably always secondary to lymphomata elsewhere—peripheral or deep glands, and spleen. The associated general features—blood, fever, cachexia, etc.—do not differ from those of the types already described.

ACUTE TYPE.—An acute form of Hodgkin's disease has also been described, in which generalization of the process and death may occur in the course of a few weeks. This acuteness may be more apparent than real, inasmuch as the process may have been localized and latent for an indefinite period in a group of nodes not discovered. The possibility of the acute course being due to secondary infection must also be borne in mind.

OTHER TYPES.—Several conditions now generally known by other names have also been looked upon by some observers as subtypes of Hodgkin's disease. Two of these in particular bear a close histological resemblance to the condition under consideration. These are *mycosis fungoides,* sometimes called *lymphogranuloma cutis,* and *Mikulicz's disease,* characterized by enlargement of the salivary and lacrimal glands.

Treatment.—Although the hope of a permanent cure in Hodgkin's disease is practically *nil,* the therapeutic régime to be followed is well defined. It consists, essentially, in **arsenic** and **radium** or the **x-ray** and the employment of symptomatic measures when called for.

MEDICINAL TREATMENT.—In a medicinal way, arsenic is our main therapeutic weapon. Although one and all of the various arsenic preparations have been employed with success in the management of the disease, the writer believes that, from the point of view of accurate dosage, freedom from by-effects and efficacy, none exceeds the oral administration of **Fowler's solution.**

No rule for the exhibition of arsenic—whichever form is employed—applicable to all cases can be formulated. In a general way, it may be said that one should begin with small doses, increasing the same to a safe maximum as a tolerance establishes itself, that the drug should be continued, if possible, until a remission is well in evidence (disappearance or well-marked reduction in size of the lymphomatous masses and spleen, and recession of the general symptoms), that the preparation should be discontinued from time to time on well-known therapeutic grounds, and that, if there are no contra-indications, it should be given periodically even during the remissions of the disease. The evidences of arsenical intolerance and poisoning—gastro-intestinal disturbances, edemas, albuminuria, various cutaneous conditions, such as exanthemata and parakeratoses, neuritides, etc.—are sufficiently well known to require no special comment.

The recognized method of administering Fowler's solution by mouth should be followed; in adults, beginning with a dose of from 2 to 3 minims (0.12 to 0.18 c.c.) three times a day, the dosage is increased by a drop *per diem* every second or third day until a total daily dose of from 20 to 30 minims (1.25 to 1.90 c.c.) is reached. Some writers advocate a maximum dosage of 50 minims (3.08 c.c.) *per diem;* however, this amount is ordinarily not needed. In the absence of contra-indicating manifestations, the maximum dosage is continued until the local symptoms (glands and spleen)—and this usually means also the associated general symptoms—have disappeared or at least greatly receded. Then the dosage may be reduced in the same proportion in which it was increased. The use of abundant **water** when the drug is taken, and at other times, considerably lessens the likelihood of toxic symptoms. This applies equally well to whatever arsenic preparation may be used. To what extent an improvement, when obtained, is due to the administration of arsenic or to the concurrent radiation of the nodes and spleen, which will be described later, is not positively known, although all the evidence is in favor of the view that arsenic plays a distinctly subsidiary rôle.

Of the other arsenical preparations which have been used in this disease there is much less known. There is really no indication for the employment of other preparations—the **trioxid,** for example—which can be administered orally. Among the forms of the drug which have from time to time been used hypodermically or intravenously, **sodium cacodylate** and **salvarsan** or **neosalvarsan** alone demand consideration, the others, such as **atoxyl** and **arsacetin,** having proved too toxic. The writer has had some experience with the cacodylate in the treatment of this disease, but none with salvarsan. The initial dose of the former should be small: from 1 to 2 grains (0.065 to 0.130 gram), administered subcutaneously two to three times a week. Later, if tolerance is indicated, the single injection may be increased to from 3 to 5 to 7½ grains (0.195-0.324 to 0.492 gram). The writer is a bit conservative about the use of the cacodylate, especially in the larger doses, having observed several serious results in the shape of a diffuse exfoliative dermatitis. In the presence of a marked and persistent garlicky breath, it is advisable to drop this method of treatment, or to decrease the dose appreciably. The principles of treatment, i.e., as to the duration of the individual courses, are similar to those mentioned in connection with Fowler's solution. The drinking of large amounts of water tends to lessen the likelihood of untoward manifestations.

Salvarsan or neosalvarsan (**arsphenamin** and **neoarsphenamin**) are administered intravenously just as in the case of syphilis, i.e., at weekly intervals, beginning with small doses. The number of injections necessary will vary considerably with the particular case. The literature bearing on the value of this preparation is too scanty to warrant a conclusion.

X-RAY AND RADIUM THERAPY.—At the present time, radiation, either by the **x-ray** or **radium**, stands assuredly in the first place in the treatment of Hodgkin's disease. The writer will not attempt to say which he considers the more efficacious, although, recently, as is natural, radium has received greater emphasis. It is probable that results obtained with the one or the other depend considerably upon the skill and experience of the operator and also, to a not inconsiderable degree, upon the types of cases which constitute a given series.

The two forms of radiation parallel one another very closely in many respects. In both, treatment is given sufficiently intensively, and sufficiently often, at first, to bring about a disappearance of the local and constitutional symptoms, and secondly, if possible, to prevent a recurrence. In both, furthermore, a secondary aim is to produce the desired results with a dosage which does not cause a systemic depression —malaise, nausea, weakness, loss of appetite, etc.—from which the patient does not recover in a few days. This depression is an evidence of intoxication produced probably by the action of a leukocytolytic ferment set free in the treatment. In both, finally, the action is exerted principally upon the lymphatic tissues themselves, which disappear to a variable degree, being replaced by connective tissue. To a certain extent the specific Hodgkin's tissue, especially the more active constituents, is also affected, the rich cellular form going over in variable degree to the fibrous stage. From another point of view radiation accomplishes the following: the lymphatic tissue upon which the Hodgkin's process grows is removed to a considerable extent by radiation; therefore, until new lymphoid tissue is formed, the specific granulomatous tissue must remain quiescent. On the basis of this last assumption, a real cure might be effected if the lymphatic structures could be permanently crippled; or, otherwise expressed, the permanence of the cure obtained by radiation depends upon how seriously the lymphatic glands and spleen have been crippled. Although, in the writer's opinion, a permanent cure is unlikely in Hodgkin's disease, because it is impossible to inhibit permanently the formation of new lymphoid tissue, or to destroy absolutely the active granulation tissue of the disease itself, it is readily admitted that with a growing experience in the use of the several radiation methods, longer and longer remissions will be obtained.

Both with radium and the *x*-ray the cases most amenable to treatment are the chronic cases, especially those with relatively little involvement of the deeper nodes; acute cases and those with marked constitutional symptoms are likely to resist this therapeutic measure. With the *x*-ray, at least, the prognosis in febrile cases is rather unfavorable. Cautious treatment of retroperitoneal lymphatic masses is indicated.

As to *technic,* no routine plan of treatment can be followed. With the *x*-ray, for example, the average method of one operator differs from that of another, both in the matter of dosage and of frequency of radiation. This is due, to a certain extent, to the apparatus itself—the various factors at the basis of dosage in one instrument producing a different effect with another instrument—and to the response of the patient to an average treatment.

In the treatment of the disease by *x*-rays, a safe average method is to irradiate three areas of nodes—or of nodes and spleen—at a sitting (nine inch tube distance, filters of 3 millimeters aluminum and one thickness of sole leather, eight inch parallel spark gap equivalent, a quantity of five milliamperes and a duration of five minutes). Other areas involved are treated at successive intervals of several days. Such a course can be repeated in from two to three weeks without causing erythema. In some cases, a pronounced systemic reaction necessitates a reduction in dosage; in others, the treatment must be more intensive. Observation of the particular case may give some idea as to the periodicity of recurrence, in which case the latter can sometimes be anticipated by radiation of the different lymph-node areas and the spleen in a series covering one or two days.

With *radium,* two types of dosage are employed: the heavy dose method and mild fractional radiation. The former seems to be particularly efficient in the chronic cases, especially when local symptoms are prominent and constitutional manifestations mild, whereas the milder, more prolonged treatment is especially suited to the acute forms and to those with acute general manifestations. The exceptions to these rules are common, demanding variations both as to dosage and frequency of radiation to meet the needs of the particular case.

Whether radium or the *x*-ray is employed, success is marked not only by the reduction in size or disappearance of the lymphomata, and the reduction in size of the spleen, but also by an amelioration of the general condition, with a gain in weight and strength, return of appetite, and a disappearance of pruritus and diarrhea, if these have been present. In the more successful cases treated by radiation, freedom from symptoms of all kinds for from three to five years has been observed in not a few instances.

SURGICAL TREATMENT.—**Surgery** in the treatment of Hodgkin's disease has few advocates. The impression is well founded that surgical intervention is not only **useless** but **harmful**, useless because, from the nature of the insinuating growth of the process along lymph-channels (not to speak of the frequent existence of deep lymph-node masses when the disease seems well localized in a single group) an attempt at radical removal is as hopeless as in the case of a similarly situated malignancy, harmful, because following operation, it frequently happens that in the same area or nearby areas the process is relighted with a greater intensity than before. It is likely that the "cures" or long remissions following operation are due to the immediate use of the *x*-ray over the field of operation. Possibly in certain cases in which pressure phenomena predominate in the clinical picture, the combination of surgery and radiation has a place, although the latter alone is generally sufficient and should first be given a thorough trial.

General and Symptomatic Treatment.—Of general and symptomatic measures, little need be said. **Rest in bed** is indicated in the acute cases, in cases with marked constitutional symptoms, and in many cases with pressure phenomena of any severity. Some patients do well on the **open-air** plan of treatment. As to **diet** there are no particular rules except that it must be nutritious and easily assimilable. **Forced feeding** has been recommended by some; but there are limitations to this régime just as in the case of tuberculosis.

Iron is often employed to relieve the anemia but probably does little good, at least when the process is active. Preparations such as **aspirin, pyramidon** and **quinin** are often serviceable for the neuralgias due to pressure. Quinin is said to be valuable in cases with high temperature curves.

In some cases, especially late in the disease, **morphin** may become necessary to relieve pain and dyspnea.

Prognosis.—The prognosis as to recovery is unqualifiedly bad; the literature contains no case which, either spontaneously or by therapeutic measures, has progressed to complete recovery. (Cures by the *x*-ray or radium, with or without preceding surgery, must be regarded as still *sub judice.*) In considering the reports of apparent complete return to health, one must bear in mind several facts: a possible mistake in diagnosis, from which the most careful and experienced observer is not free, the occasional variation from the average clinical picture, especially of the first stage (three, five, seven, even fifteen and seventeen years); and the possibility of recurrence even after many years of quiescence.

The duration of the disease as a whole, and of the several stages, has already been sufficiently commented upon. A number of factors, not subject to forecast, affect the outlook in the particular case. The duration of the stage of localization—the latent period—varies considerably; generalization, when it begins, may be slow and orderly or rapid and stormy; secondary infections—pyogenic, tuberculous—are frequent and serious; life-threatening compression phenomena are not predictable; and the apparent quiescence of the visible nodes is no criterion of the glands deeply situated.

Symptoms pointing to an early fatal outcome, therefore, are the beginning of the period of generalization, especially when the spleen and liver become involved, pressure phenomena involving important structures, and fever, the more continuous type, indicating relentless progress of the Hodgkin's process, and the remittent and recurrent types pointing to superimposed infections. Primary or early involvement of the deeply situated nodes generally indicates a short course. Remissions are common and characteristic, and are due partly to treatment, and are, in part, apparently spontaneous—to some degree, therefore, calling into question the effect of treatment. Surgical procedures are frequently followed by a flareup at the site of operation, more virulent than the condition in the nodes previous to their removal, and a rapid generalization of the process. To a certain extent this can be prevented by *x*-ray or radium treatment of the operative field.

Despite the gloominess of the foregoing prognosis, one is impressed by the long-continued freedom from signs and symptoms brought about in certain cases by a wise employment of the *x*-ray or of radium.

Pathological Anatomy.—What is known of the *pathogenesis* of Hodgkin's disease has been discussed in connection with the etiology. (*See* page 110.)

MACROSCOPIC CHANGES.—*Lymphatic System.*—The strictly clinical appearances of the lymph-nodes—size, consistency, relation to one another and to their environment—were considered in detail under the heading Symptomatology (page 116). In this place, suffice it to say that the degree of involvement of the *lymph-glands* may vary from that of relative localization in one group, or several groups, to the most extensive generalization; that the individual glands tend to remain discrete, even after they have individually attained a very considerable size, and that a matting together or an adherence to the skin nearly always indicates secondary infection of some sort; that the individual nodes are generally regular in contour and round or oval in shape; that, as a rule, the younger glands are soft and elastic and the older ones firm or even hard (late fibrous changes), though the reverse may be true; that actual softening or sinus formation is an evidence of superimposed pyogenic or tuberculous infection; that the lymphomatous masses may be composed of innumerable small nodes or of a varying number of small and large tumors; and that the masses are subject to considerable variation from time to time, both in size and consistency, as a result, it is thought, of varying pressure effects exerted upon the lymph-channels.

In the extension of the process the specific *granulation tissue* establishes itself in preformed or new nodes immediately adjacent to one of the older glands or at a variable distance from the latter. In some cases the growths form bead-like prominences along the lymphatic channels connecting one gland group with another; in others there is no evident pathology in the channels between one set of glands and another. In the growth of the granulomatous masses, the newly formed members push forward between the muscle-fibers or push muscles and other structures aside, but do not invade them as do malignant affairs.

Involvement of the spleen and of non-lymphatic organs occurs by way of the lymphatic circulation. They are probably not true metastases, but lymphomata arising from the lymphoid tissues of the organ involved.

On section, the lymph-nodes exhibit a variable appearance, depending upon the stage of the disease. Early, the color is gray—more opaque than the normal—and the surface bulges somewhat, while in the older cases the grayish appearance is variegated by depressed bands of yellow representing connective-tissue formation. Hemorrhagic points are sometimes seen, as are also minute yellowish or grayish areas due to focal necrosis. In the far-advanced cases the yellow color due to fibrous changes may displace the gray of the early stages.

As regards the metastases in the spleen and other organs—and apparently these may appear wherever lymphoid tissue is normally found—one feature in particular demands emphasis, namely that they form *nodules* and not diffuse infiltrations as do certain of the leukemias, for example. In appearance they do not differ essentially from the lymph-nodes; they are grayish-white in color, vary in size from pinpoint or microscopic lesions to large nodules, and are well marked off from the surrounding tissues. The other, essentially clinical, characteristics of these organ metastases have been discussed.

MICROSCOPIC CHANGES.—Reed, in the conclusion of her studies on "The Pathological Changes in Hodgkin's Disease," says that "Hodgkin's disease has a peculiar and typical histological picture, consisting of proliferations of the endothelial and reticular cells, formation of lymphoid cells, and characteristic giant-cells and a gradual increase in the amount of connective tissue, resulting in fibrosis, and in most of the specimens, in the presence of great numbers of eosinophils." This résumé expresses briefly and clearly our present understanding of the tissue changes, upon the basis of which a diagnosis of Hodgkin's disease is justified.

Various Stages.—For convenience of description the histological changes in this disease may be divided into three stages. This subdivision is purely arbitrary, as the several periods overlap freely and regularly. What will be designated as the second period is the most striking and, in a way, the most characteristic of the three; to the initiated, however, the early and terminal stages are equally characteristic and should be thoroughly understood, inasmuch as it not infrequently happens that a diagnosis must be made on the basis of tissue representing wholly, or in great part, the changes of these initial and final periods, in which little of the more typical cellular pathology may be seen.

The *first stage* covers the very beginnings of the disease as represented by the smallest glands; it is roughly coincident with the disappearance of the identity of the lymph-follicle. The earliest changes observed in such nodes are a proliferation of the large cells compos-

Fig. 6.—Hodgkin's Disease. Lymph-node. The various cell types characteristic of the disease are seen in this section, although the granules of the eosinophiles are not well produced. x 325. (Figs. 6, 7, 8 and 9 appeared in an article by the author—Some Aspects of Hodgkin's Disease—which appeared in the "Medical Clinics of North America," Vol. III, page 215. Reproduced by courtesy of W. B. Saunders Company.)

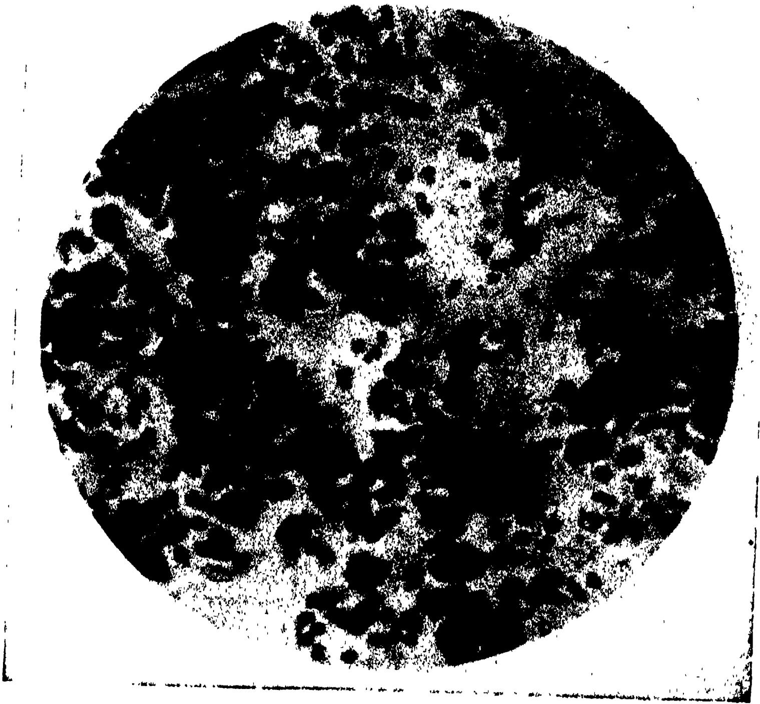


FIG. 7.—HODGKIN'S DISEASE. A higher magnification of a portion of Figure 6. x 450.

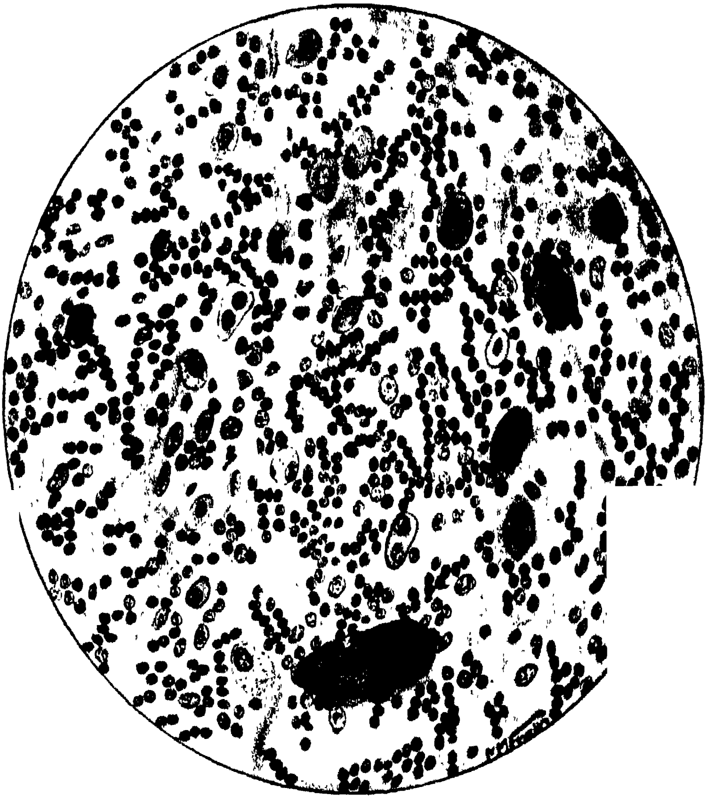
ing the germinal centers of the lymph-follicles and of the flat cells of the reticular endothelium, which often show mitotic figures. In addition, there is generally an increased vascularity and a dilatation of the lymph-sinuses. As the condition progresses the dilated sinuses and the spaces in the reticulum become more and more filled with these hyperplastic lymphoid and endothelial cells, the typical structure of the lymph-follicle is blotted out, and stage one passes over into stage two, characterized by its rich cellular complex. According to Ziegler and others, however, certain cases deviate from the course just described in that the early lymphoid hyperplasia is never displaced by cellular proliferation of other types, though the end stage, fibrosis, is the same in all forms. It is this lymphoid type which is especially apt to cause difficulty in excluding such conditions as tuberculosis, leukemia, etc.

In the well-defined *second stage* (*see* Plates I and II and Figs. 6 and 7) the microscope shows a most varied cell-picture. Filling the spaces of the reticular meshwork, with no structural arrangement, are large epitheloid cells with vesicular nuclei; derivatives of the proliferating endothelium, unusually large epithelioid cells with one or more nuclei (giant-cells), standing out prominently in the section even under low magnification, epithelioid cells undergoing lively mitosis, large and small lymphocytes, eosinophils, polynuclear leukocytes and plasma-cells. Occasionally, giant-cells with peripherally situated nuclei are also seen. In some cases, the distribution of these various cells may be fairly uniform throughout the tissue; in others a high magnification shows that they tend to become grouped, with clumps of epithelioid cells in one place, of eosinophils in another and of lymphoid cells in still another.

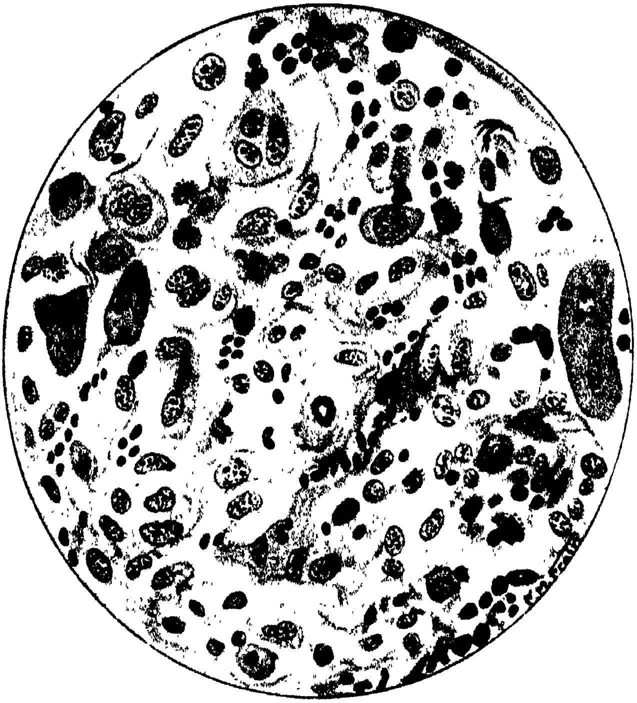
This may be called the typical picture of the second stage. The average section, however, even at this period, shows transitions both of the early and to the later phases. Indicative of the former stage are remnants of the lymph-follicles and relics of the lymph-sinuses, and of the latter the ever-increasing amount of reticular tissue which, in its growth, becomes thicker, breaks up the cellular monotony by the formation of cell islands, and gradually progresses to the connective-tissue predominance of the third stage.

As another late phase of the intermediate period one may cite the appearance of areas of necrosis of variable size. Due to anemia (anemic necrosis), portions of the cellular complex undergo degeneration and exhibit the usual evidence of this pathological change, namely broken-down cells, fragmented nuclei, etc. Fibrous bands often enclose such areas, which may contain a few of one or the other of the typical cell types described. Macroscopically, and microscopically, such areas differ fundamentally from caseation.

The *third and final stage* of the histological process is represented by an ever-increasing growth of connective tissue, the beginnings of which were noted in the intermediate period. (*See* Plate III and Figs. 8 and 9.) Now, instead of isolated fibrous bands weaving in and out and enclosing large islands of cells, one observes considerable areas of connective tissue in which there are scattered cells, particularly of lymphocytic

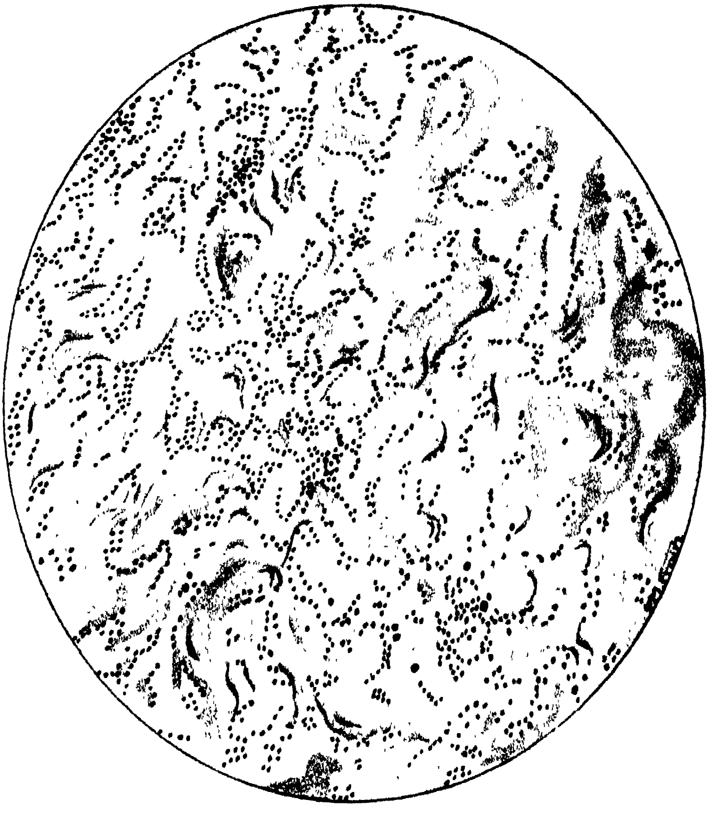


Hodgkin's Disease. Section of Lymph-Node Showing the Cellular Complex Characteristic of the Disease. Lymphocytes, Epithelioid Cells, Multinucleated Giant-Cells and a Few Eosinophils. Evidence of Proliferating Reticular Tissue.



Hodgkin's Disease. A Section of Lymph-Node, Highly Magnified, Showing the Typical Cell-Complex of the Disease. Eosinophils are Numerous and a Mitotic Figure is Seen in the Center of the Section. A Proliferation of the Reticulum is also Evident.

PLATE III.



Hodgkin's Disease. Lymph-Node. Stage of Fibrosis. Enmeshed in the Fibrous Strands, Which in Part Have Undergone Hyalin Degeneration, are a Few Cellular Elements, Chiefly Lymphocytes.

character, although occasionally one or more of the more characteristic types—eosinophilic or large epithelioid—may be present. Hyaline changes in the connective tissue are frequently observed as a later degenerative process.

We have already called attention to the marked diversity in the histological pictures of the early and late phases of Hodgkin's disease. The preceding descriptions of the same emphasize the importance of a thorough understanding of the several steps in the tissue changes in order that a diagnosis may be made at any period.

Types of Cells.—The essential pathology of the disease will perhaps be better grasped by a final brief reference to the several types of cells which go to make up the specific tissue. The specific cell of the granuloma, if one may thus speak of any type, is the *endothelial cell.* The very beginnings of the disease, as far as we are able to say, are represented by a proliferation of the reticular endothelium and of the lymphoid cells in the germinal centers of the follicles. According to Reed, these lymphoid cells and the endothelial cells just mentioned are presumably identical. The growth of these cells is a very active one, and mitotic figures are a characteristic component of the tissue. A later phase of this same endothelial hyperplasia is the appearance of mononuclear and multinuclear giant-cells. The former are generally conceded to be derived from the reticular endothelium; and the giant types are derived from those with a single nucleus. The larger giant-cells are generally irregular in form, contain a clear cytoplasm, and have a pale nucleus which is large in proportion to the size of the entire cell. The nucleus may be round, bean-shaped, or of most bizarre contour. The individual cell may contain a single such nucleus or as many as from eight to ten, which are characteristically arranged in the center of the cell. A peripheral arrangement, suggesting the tuberculous giant-cell, is occasionally seen; the origin of this type is attributed by Reed to a coalescence of the stroma cells. In periods of rapid growth these cells may give rise to syncytial plaques. "These giant-cells, as far as our observation reaches, are peculiar to this growth, and are of great assistance in diagnosis" (Reed).

The *lymphoid cells* which form a prominent feature of the early phase of the disease are, for the most part, of the small type, although larger forms are not uncommon. They arise, it is presumed, both from the reticular endothelium and from the germinal centers of the lymph-follicles. In some cases, as we have already observed, lymphoid hyperplasia persists until the final stage of fibrosis. Often, lymphoid proliferation is coincident with a relative lymphocytosis of the circulating blood.

Eosinophilic cells, morphologically similar to those of the blood, are a very frequent component of the Hodgkin's tissue. Although they may be seen at any point in the gland, the site of predilection seems to be the periphery. These cells show none of the evidences of participation in the specific cellular hyperplasia—no mitoses, for example—and are generally regarded as cells which are attracted to the tissue by some

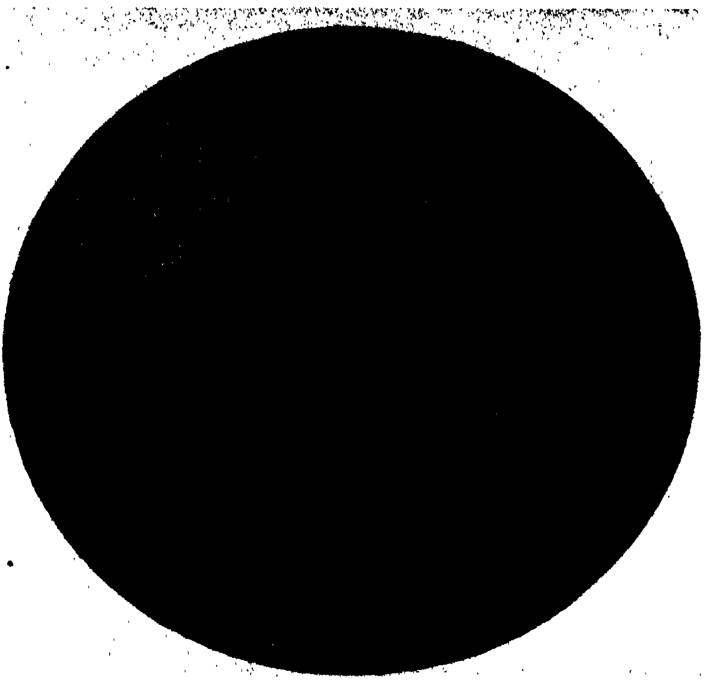


FIG. 8.—HODGKIN'S DISEASE. A section of lymph-node illustrative of well-advanced changes. To a great extent hyalin connective tissue has replaced the cellular elements. Among the latter a few of the large type are still evident. x 115.

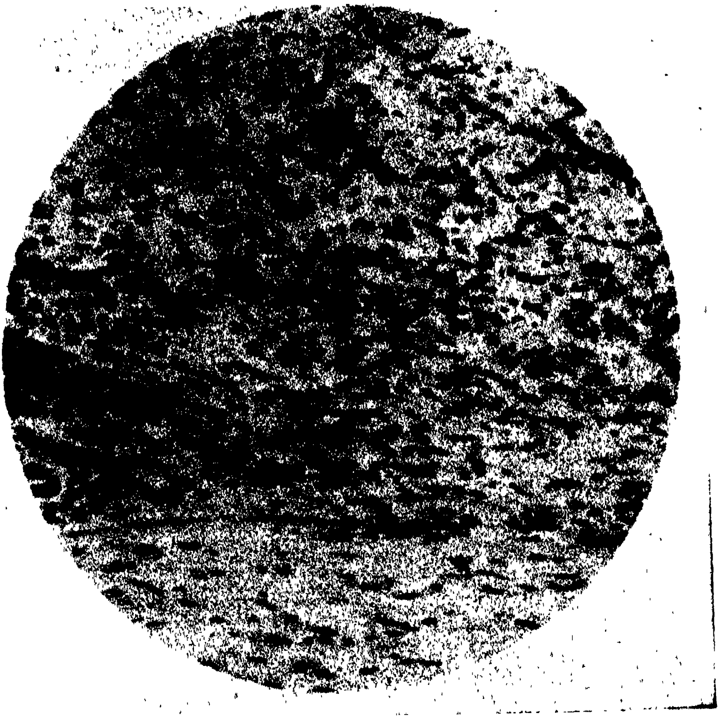


Fig. 9.—Hodgkin's Disease. A section of a lymph-node showing phases in the fibrous metamorphosis. Above is seen a multinucleated giant-cell. x 230.

chemotactic substance contained in the latter. Blood eosinophilia is frequently associated with tissue eosinophilia, and both are of great importance in diagnosis.

Plasma cells are observed in some tissues in great numbers. Their origin is probably the same as that of the lymphocytes. *Polymorphonuclear leukocytes* do not form a striking component of the specific Hodgkin's tissue; however, in secondary pyogenic infection involving the nodes they may be present in great numbers.

The nodules in the spleen and in non-lymphatic organs arise and progress as do those just described. In some cases they are miliary in character, or even microscopic; in others, they form large irregular masses, by growth and by coalescence.

Coincident tuberculosis may occur in the Hodgkin's nodes either in miliary form, single or conglomerate, or in the form of caseous areas of variable size.

BIBLIOGRAPHY *

ALDERSON. Cutaneous metastases in Hodgkin's disease. Jour. Cutan. Dis., 1917, xxxv, 481.

BENDA. Zur Histologie der pseudoleukämischen Geschwülste. Verhandl. d. Deutsch. path. Gesellsch., Berlin, 1904, vii, 123.

BILLINGS AND ROSENOW. Etiology and vaccine treatment of Hodgkin's disease. Jour. Am. Med. Assn., 1913, li, 2122.

BILLINGS. Focal infection. New York and London, 1916.

BLOOMFIELD. The bacterial flora of lymphatic glands. Arch. Int. Med., 1915, xvi, 197.

BLUMBERG. Über der Lymphomatosis (Paltauf-Sternberg). Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1912, xxiv, 516.

BUNTING. Blood-platelets and megalokaryocytes in Hodgkin's disease. Johns Hopkins Hosp. Bull., 1911, xxii, 114.

——— The blood-picture in Hodgkin's disease. Johns Hopkins Hosp. Bull., 1911, xxii, 369.

The blood-picture in Hodgkin's disease (Second paper). Johns Hopkins Hosp. Bull., 1914, xxv, 173.

Diphtheroid infection. Johns Hopkins Hosp. Bull., 1915, xxvi, 179.

BUNTING AND YATES. Cultural results in Hodgkin's disease. Arch. Int. Med., 1913, xii, 236.

——— An etiologic study of Hodgkin's disease. Preliminary note. Jour. Am. Med. Assn., 1913, lxi, 1803.

——— An etiologic study of Hodgkin's disease. Second note. Jour. Am. Med. Assn., 1914, lxii, 516.

——— Hodgkin's disease. Johns Hopkins Hosp. Bull., 1914, xxv, 177.

——— Results of treatment of Hodgkin's disease. Jour. Am. Med. Assn., 1917, lxxviii, 701.

——— Bacteriological results in chronic leukemia and in pseudoleukemia. Johns Hopkins Hosp. Bull., 1915, xxvi, 376.

——— Leukemia and pseudoleukemia. Johns Hopkins Hosp. Bull., 1917, xxviii, 151.

BURNAM. Treatment of Hodgkin's disease. Surg., Gynec. and Obst., 1919, xxviii, 440.

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* No attempt has been made to offer an exhaustive bibliography. The list given includes selections of the older and more fundamental articles, on the one hand, and of the more representative recent ones on the other.

Byfield. The present status of Hodgkin's disease. Am. Jour. Med. Sc., 1918, clv, 409.

——— Some aspects of Hodgkin's disease. Med. Clin. North America, 1919, iii, No. 1, 215.

Cohnheim. Ein Fall von Pseudoleukämie. Arch. f. path. Anat., 1865, xxxiii, 451.

Cole. Cutaneous manifestations of Hodgkin's disease. Jour. Am. Med. Assn., 1917, lxix, 341.

Coley. Further evidence in support of the theory that Hodgkin's disease is a type of sarcoma. Tr. Am. Surg. Assn., 1908.

——— A report of recent cases of inoperable sarcoma treated with mixed toxins of erysipelas and *Bacillus prodigiosus*. Surg., Gynec. and Obst., 1911, p. 174.

——— Primary neoplasms of lymph-nodes including Hodgkin's disease. Ann. Surg., 1916, xii, 323.

Cunningham. Hodgkin's disease and diphtheroids. Am. Jour. Med. Sc., 1917, cliii, 406.

Delafield. A case of acute and fatal tuberculosis of the lymphatic glands. Med. Rec., 1887, xxxi, 424.

Ebstein. Das chronische Rückfallsfieber, eine neue Infectionskrankheit. Berl. klin. Wchnschr., 1887, xxiv, 565.

Evans. Observations on the origin and status of the so-called "transitional" white blood-cell. Arch. Int. Med., 1916, xvii, 1.

Fischer. Über der Hodgkinsche Krankheit (Lymphomatosis granulomatosa). Ztschft. f. Hygiene., 1910, lxvii, 159.

Fox. Studies in diphtheroids. III. Bacteria isolated from enlarged glands, especially in Hodgkin's disease. Arch. Int. Med., 1915, xvi, 465.

Fraenkel. Über der sogenannten Hodgkinsche Krankheit (Lymphomatosis granulomatosa). Deutsch. med. Wchnschr., 1912, No. 14, 637.

Fraenkel and Much. Bemerkungen zur Ätiologie der Hodgkinsche Krankheit und der Leukämia lymphatica. Munchen. med. Wchnschr., 1910, No. 13, 685.

——— Über malignes Lymphom. Arch. f. klin. Chir., 1897, lv, 467. Also Deutsche (Chirurgie, 1901, Lieferung 24A).

Gibbons. The relation of Hodgkin's disease to lymphosarcoma. Am. Jour. Med. Sc., 1906, cxxxii, 694.

Hirschfeld. Die Pseudoleukämie. Ergebn. d. inn. Med. u. Kinderh., Berlin, 1911, vii, 161.

Hodgkin. On some morbid appearances of the absorbent glands and spleen. Med.-Chir. Tr., 1832, xvii, 68.

Howell. Acute Hodgkin's disease. Practitioner, 1917, xcix, 565.

Irons. Hodgkin's disease. In Forchheimer's: Therapeusis of internal diseases, New York and London, 1914, v, 665.

Janeway. Hodgkin's disease with extensive skin eruption. Med. Clin. North America, 1917, i, 1.

Karsner. A study of cases of Hodgkin's disease and certain allied conditions. Arch. Int. Med., 1910, vi, 175.

Kusunoki. Zur Ätiologie der Lymphomatosis granulomatosa. Virchow's: Arch. f. path. Anat., 1914, ccxiv, 184.

Levin. Roentgen-ray and radium treatment of Hodgkin's disease. Med. and Surg., 1917, i, 411.

Longcope. Hodgkin's disease. In: Osler and McCrae's System of medicine, 2nd edit., 1915, vi, 755.

——— On the pathological histology of Hodgkin's disease, with a report of a series of cases. Bull. Ayer Clin. Lab., 1903-1904, pp. 14-76.

Mellon. A case of splenic Hodgkin's disease. Am. Jour. Med. Sc., 1916, cli, 704.

Moore. Immunologic studies on Hodgkin's disease. Jour. Infect. Dis., 1916, xviii, 569.

Morawitz. Die Hodgkinsche Krankheit. In: Handbuch der innere Medizin, 1912, iv.

Moritz. Über akute Pseudoleukämie. St. Petersburg med. Wchnschr., 1906, xxxi, 419.

Murray. Lymphadenoma. In: Albutt's System of medicine, 8th edit., London, 1908, iv, Part 1, p. 459.

Musser. Notes on the fever of Hodgkin's disease; recurrent (Rückfall) fever; Ebstein's disease. Am. Med., 1902, iii, 13.

de Negri and Mieremet. Zur Ätiologie der malignen Granuloms. Centralbl. f. Bakteriol., Orig., 1913, lxviii, 292.

Naegeli. Blutkrankheiten und Blutdiagnostik, 1912, 2nd edit., 187.

Oliver. The relation of Hodgkin's disease to lymphosarcoma and endothelioma. Jour. Med. Research, 1913, xxix, 191-207.

Osler. On splenic anemia. Am. Jour. Med. Sc., 1900, cxix, 54.

——— On splenic anemia (second paper). Am. Jour. Med. Sc., 1902, cxxiv, 751.

Paltauf. Lymphosarkom (Lymphosarkomatose, Pseudoleukämie, Myelom, Chlorom). Ergebn. d. allg. Path. u. path. Anat., 1897, iii, 652 (literature).

——— Die lymphatischen Erkrankungen und Neubildungen der Haut. Die Mycosis fungoides. In: Mrâck's Handbuch der Hautkrankheiten., 1909, iv, Part 2, 681.

Pel. Pseudoleukämie, oder chronische Rückfallsfieber. Berl. klin. Wchnschr., 1887, xxiv, 644.

——— Zur Symptomatologie der sogenannten Pseudoleukämie. Berl. klin. Wchnschr., 1885, xxii, 3.

Pinkus. Pseudoleukämie. In: Nothnagel's System.

——— Hautveränderungen bei Pseudoleukämien. In: Kraus-Brugsch Spez, Pathol. u. Therap. inn. Krankh., 1915, viii, 331.

Pusey. Cases of sarcoma and of Hodgkin's disease treated by exposures to *x*-rays. A preliminary report. Jour. Am. Med. Assn., 1902, xxxviii, 166.

Reed. The pathological changes in Hodgkin's disease. Johns Hopkins Hosp. Rep., 1902, x, 133 (literature to 1902).

Rosenow. The newer bacteriology of various infections as determined by special methods. Jour. Am. Med. Assn., 1914, lxii, 903.

Senator. Die Pseudoleukämie. In: Modern Clinical Medicine.

Simmons. Hodgkin's disease. Jour. Med. Research, 1903, ix (n. s.), 378.

Simmons and Benet. Report on cases of Hodgkin's disease observed at Collis P. Huntington Memorial Hospital. Boston Med. and Surg. Jour., 1917, clxxvii, 819.

Steiger. Blutbefunde bei Lymphogranulomatosis (Paltauf-Sternberg). Berlin. klin. Wchnschr., 1913, l, 2129.

——— Klinik u. Pathologie der Lymphogranulomatosis (Paltauf-Sternberg). Ztschr. f. klin. Med., 1914, lxxix, 452.

Sternberg. Über eine eigenartige, unter dem Bilde der Pseudoleukämie verlaufende Tuberkulose des lymphatischen Apparates. Ztschr. f. Heilk., 1898, xix, 21.

——— Universelle Primärerkrankungen des lympatischen Apparates. Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1899, ii, 641, 711, 770, 813, 847.

Symmers. Certain unusual lesions of the lymphatic system, including a description of primary Hodgkin's disease and a case of gastro-intestinal pseudoleukemia. Arch. Int. Med., 1909, iv, 218.

——— Hodgkin's disease. Interstate Med. Jour., 1917, xxiv, 982.

——— Pathologic histology of Hodgkin's disease. Arch. Int. Med., 1917, xxix, 990.

Türk. System der Lymphomatosen. Wien. klin. Wchnschr., 1903, xvi, 1073.

Virchow. Die krankhaften Geschwülste. 1864, ii, 728.

VERPLOEGH, KEHRER AND HOOGENHUYZE. Bakteriologische Befunde bei Lymphogranulomatosis. München. med. Wchnschr., 1914, lxi, 1158.

WADE. Primary Hodgkin's disease of the spleen (Dorothy Reed type). Jour. Med. Research, 1913, xxix, 209.

WARFIELD AND KRISTJANSON. Hodgkin's disease of the intestines. Johns Hopkins Hosp. Bull., 1916, xxvii, 24.

WARNECKE. Über die Hodgkinsche Krankheit. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1905, xiv, 275.

WARRINGTON. A case of acute Hodgkin's disease, with remarks on the diagnosis. Liverpool Med.-Chir. Jour., 1915, xxxv, 257.

WHITE. A clinical lecture on some cases of enlarged lymphatic glands. Clin. Jour., London, 1906.

WHITE AND BOYCOTT. A case of Hodgkin's disease with peculiar blood changes. Jour. Path. and Bacteriol., xiv, 402.

WILKS. Cases of a peculiar enlargement of the lymphatic glands frequently associated with disease of the spleen. Guy's Hosp. Rep., 1856, ii, 114; *Ibid.,* 1865, xi, 56.

——— Enlargement of the spleen and lymphatic glands. Tr. Path. Soc., London, 1859, x, 259.

YAMASAKI. Zur Kenntnis der Hodgkinsche Krankheit und ihres Überganges in Sarkom. Ztschr. f. Heilk., 1904, xxv, 269.

YATES. A clinical consideration of Hodgkin's disease. Johns Hopkins Hosp. Bull., 1914, xxv, 180.

——— Etiology, pathology and therapy of Hodgkin's disease. Colorado Med., 1916, xiii, 39.

ZIEGLER. Die Hodgkinsche Krankheit. Jena, 1911 (very complete literature).

——— Granulierende Pseudoleukämien der lymphatischen Apparates inklusive Morbus Mikulicz. In: Kraus und Brugsch's Spec. Path. u. Therap. inn. Krankh., Berlin u. Wien, 1915, viii, 106

CHAPTER XLVII

DISEASES DUE TO NEMATHELMINTHES

By Eugene R. Whitmore, B.S., M.D.

Nematoda, p. 159:—Nematodes in the digestive tract, p. 160:—Ascariasis, p. 160; Oxyuriasis, p. 168; Ancylostomiasis, p. 172; Trichuriasis, p. 173; Trichiniasis, p. 175; Strongyloidiasis, p. 187; Nematodes in the blood and lymph, p. 189:—Filariasis, p. 190:—Filarial lymphangitis, p. 195; Lymphatic tumors, p. 196; Lymphorrhagia, p. 197:—Internal lymphorrhagia, p. 197—External lymphorrhagia, p. 198—Elephantiasis, p. 198—Other filarial infections, p. 207:—Filaria demarquayi, p. 207—Filaria (microfilaria) tucumana, p. 207—Filaria (agamofilaria) conjunctivæ, p. 207—Thelazia pallipæda, p. 207—Loa loa, p. 208—Onchocerca volvulus, p. 211—Acanthocheilonema perstans, p. 214—Dirofilaria magalhæsi, p. 215—Dirofilaria immitis, p. 215—Nematodes in the subcutaneous tissues, the embryos not passing into the blood, p. 216:—Dracunculus medinensis, p. 216—Nematodes in the lungs, p. 219:—Metastrongylus elongatus, p. 219—Nematodes of the kidneys, p. 219:—Dioctophyme renale, p. 219.
Acanthocephala, p. 220.
Gordiacea, p. 220.

Three classes of the phylum Vermes are of importance to the medical man, as indicated by the following table from Brumpt:

A. No Ventral Nervous Chain
    1. No prebuccal ciliary apparatus
        (*a*) Body flat .... Platyhelminthes
        (*b*) Body cylindrical .... Nemathelminthes
B. Having a Ventral Nervous Chain ...... Annelides

The nemathelminthes, or round worms, are divided into three orders, as indicated in the following table from Brumpt:

A. Having a Digestive Tube
    1. Complete .... Nematoda
    2. Atrophied in the Adult .... Gordiacea
B. No Digestive Tube .... Acanthocephala

I. NEMATODA

The nematodes are by far the most important order of the round worms. They are slender, round worms, with a complete digestive tube

They are never segmented, though the surface may show irregular annulations which do not correspond to internal segmentation. The sexes are separate.

For the practical purposes of the medical man, it is convenient to study the nematodes according to the part of the body in which they live, as indicated in the following:

A. Nematodes in the Digestive Tract:
   1. Ascariasis
   2. Oxyuriasis
   3. Ancylostomiasis
   4. Trichuriasis
   5. Trichiniasis
   6. Strongyloidiasis

B. Nematodes in the Blood and Lymph:
   1. Filariasis

C. Nematodes in the Subcutaneous Tissues:
   1. Dracontiasis

D. Nematodes in the Viscera

A. NEMATODES IN THE DIGESTIVE TRACT

(*a*) FAMILY ASCARIDIDÆ

In this family of worms, the body is thick, and the mouth has three more or less developed oral papillæ. Two genera are of importance: Ascaris and Oxyuris.

1. Ascariasis

Definition.—Ascariasis is the name given to the condition resulting from the development of *Ascaris lumbricoides* (eelworm, roundworm) in the intestine.

Etiology.—PREDISPOSING CAUSES.—*Climate.*—Infestation with the worm is more common in the tropics and in moist regions; and in temperate climates the conditions are more favorable for infection in the warm season.

Season.—In the southern part of the United States the infection is more evident in the summer and fall; but Deaderick thinks this is due to the fact that this is the malarial season, and that febrile conditions cause wandering and expulsion of the worm.

Soil.—Infestation is more common in persons who are liable to take contaminated soil into the mouth. Children, miners, and persons who work in the soil are most liable to infection. It is more common in rural districts than in cities.

Age.—Age is an important factor. While the greater exposure of children to infection by contaminated soil would in part account for the greater frequency of infection among them, the young of all animals show a greater susceptibility to worm infections than do the adults. This is especially well seen in dogs and cats, where the young and the adults live under the same conditions: the young harbor numerous worms, while the adults have only an occasional worm. In 534 cases collected by Stiles and Garrison, over 83 per cent. were children under fifteen years of age. In some parts of the tropics and subtropical regions, children are given a vermifuge once a year.

Race.—Deaderick says that negroes are more often infested than are whites, and that females are more prone to infestation than males. It is difficult to say whether this is a race and sex predisposition or is dependent merely on greater opportunity for infestation. In Lucke's examinations of healthy soldiers, 18 to 42 years of age, the infection was over nine times as common in whites as in negroes (4.82 per cent. in whites, and 0.51 per cent. in negroes) and Lucke considers that the difference is due to race.

EXCITING CAUSE.—*Ascaris lumbricoides* Linnaeus, 1758, is the common cause of the condition. *Ascaris lumbricoides* is identical with, or is closely related to, *Ascaris suum* (or *Ascaris suilla*), the common roundworm of the pig.

(*a*) *Morphology.*—*Ascaris lumbricoides* is reddish-brown or grayish-yellow in color. The female is from 20 to 25 centimeters (from 8 to 10 inches) long, and 0.5 centimeter (1/5 inch) in diameter; the male is from 15 to 20 centimeters (from 6 to 8 inches) long, and 0.3 centimeter (1/8 inch) in diameter. The body is stiff and elastic, pointed at the two ends. The head is small and bears three lips with finely dentated margins, the dorsal lip having papillæ at its base, the other lips having a single papilla. The male has the tail end curved and rolled up, and the two unequal spicules are readily seen; in the female the vulva is in the anterior third of the body.

(*b*) *Habitat.*—The worm normally lives in the small intestine, males and females living together in approximately equal numbers.

The number of worms is variable: there are usually five or six worms in the small intestine; but the number may be large—even up to 1,000—and there are cases in which a child has passed up to 5,000 ascarides in a period varying from a few months to a few years.

(*c*) *Evolution.*—A single female passes thousands of eggs, which are passed out with the feces of the host. The eggs are ellipsoid, 50 to 75 microns (1/500 to 1/360 inch) long, and 40 to 60 microns (1/625 to 1/420 inch) in diameter; the shell is smooth, and is surrounded by an albuminous membrane which is irregularly mammillated. The eggs are white when passed from the female, but they become brown in color as they pass down the intestine, mixed with the feces.

The egg contains a single cell when passed out with the feces. Under favorable conditions of temperature, moisture and oxygen supply, the embryo develops within the eggshell until it comes to be a coiled-up worm; this development requires 14 to 30 or 40 days, depending upon the conditions in the surrounding medium. Water and moist earth are the most favorable media for the development of the embryo. Yoshida and Hotta found that the embryo does not develop in urine.

The developed embryo, within the highly impermeable eggshell, is very resistant, and remains alive for a long time—five years or longer. It is not killed by drying, exposure to the sun, or freezing for a period of several months. Yoshida and Hotta found that phenol kills the embryo, but that strong chemicals—as mineral acids—do not prevent development of the embryo, as they coagulate the albuminous envelope of the egg, and the embryo is protected.

The eggs do not hatch, except accidentally, outside the body of a host; and when they do hatch outside, the embryo quickly dies. When swallowed by a mammal, the fully developed eggs hatch in the small intestine and the embryo is set free as a larva. The hatching is due to the action of the embryo and not to a simple digestion of the eggshell; and fully developed eggs will hatch if placed under the skin. The eggs do not hatch unless the embryo is fully developed.

In five or six weeks after the swallowing of fully developed eggs, adult worms are found in the small intestine of the host; and for many years it was supposed that the embryo escaping from the egg in the small intestine developed directly into the adult worm, without any migration. In 1916, Stewart reported the results of some experiments in feeding fully developed ascaris eggs to rats and mice. He found that, after the eggs hatch in the small intestine of mice or rats, the larvæ penetrate the wall of the intestine and pass to the liver and lungs, developing as they go. After reaching the lungs, the larvæ were found in the bronchi, trachea, mouth, stomach, small intestine and feces of the rats and mice. As the worms did not develop in passing through the intestinal tract of rats and mice, Stewart concluded that rats and mice acted as intermediate hosts for the development of the worm and that the immature worms which were passed in the feces of the rats and mice, or were contained in their saliva, gained access to water and food, and so reached the small intestine of man, where they developed to adult worms.

Ransom and Foster confirmed Stewart's findings but did not agree with his conclusion that rats and mice acted as intermediate hosts for the worms. They concluded that the migration and development in the liver and lungs, and return to the intestine, was the normal cycle of development of the worm; but the failure to develop to the adult worm, after returning to the small intestine of rats and mice, was due to the fact that those animals were not suitable hosts for the worm. By feeding ascaris eggs to a lamb, a kid and pigs, Ransom and Foster showed that the entire cycle of development—from the hatching of the fully developed egg to the adult worm—takes place in the one host, the migration to the liver and lungs and the return to the small intestine by way of the trachea and esophagus being a part of the cycle of development. The fully developed egg hatches in the small intestine of experimental animals in 12 to 19 hours; and the larvæ appear in the liver as early as two days after the eggs are swallowed. They appear in the lungs as early as three days, and are numerous there in seven to ten days after the eggs are swallowed. They are found in the small intestine as early as six days, and numbers are passing down the esophagus eight to ten days after the eggs are swallowed. The newly hatched larva is about 0.25 millimeter (1/100 inch) long; and on its return to the small intestine, after its migration through the liver and lungs, it is 1.5 to 2.5 millimeters (3/50 to 1/10 inch) long. During its migration the larva undergoes considerable change in structure and molts at least twice.

On the basis of these experimental findings, the cycle of development of ascaris in man is as follows: The larvæ, liberated by the hatching of the fully developed eggs in the small intestine, penetrate the wall of the intestine and pass in the blood stream to the liver; and, after remaining a few days in the liver, they pass in the blood stream to the lungs, where they are stopped in the capillaries and undergo further development. From the lung capillaries they pass to the air vesicles and bronchioles; up the bronchi and trachea; down the esophagus, and through the stomach to the small intestine, where they develop to adult male and female worms. The period, from the time the fully developed eggs are swallowed to the appearance of adult worms in the small intestine, is five or six weeks.

Other Species of Ascaris.—Less commonly, other species of ascaris are found in the intestinal tract of man.

Ascaris maritima (Leuckart, 1876) and *Ascaris texana* (Smith and Goeth, 1904), have been reported from Greenland and Texas respectively.

Belascaris Leiper, 1907, has two lateral, wing-like membranes on the anterior end. *Belascaris mystax* (Zeder, 1800) is the common ascaris of the cat, and it has been reported in man.

Toxascaris Leiper, 1907, has the lateral, wing-like membranes longer and narrower than in Belascaris. *Toxascaris limbata* (Railliet and Henry, 1911) is the common ascaris of the dog, and it has been found once in man.

Epidemiology.—The conditions favoring the development of the worms outside the body are warmth and moisture, as in the tropics and in mines. The eggs, passed in the feces and developed in water or moist earth, are taken into the mouth with contaminated food or water, or on the hands soiled with dirt containing the eggs. The eggs withstand drying, and may contaminate food by being blown about with dust. As the eggs withstand freezing for some time, they can pass through the winter outside the body of the host. Flies would not seem to play any important part in the spread of the infection, on account of the long period of development necessary before the eggs can complete their development in man. For the same reason, auto-infection is not possible.

Symptomatology.—Not infrequently there are no symptoms, even when a number of worms are present in the small intestine. Commonly there are gastro-intestinal symptoms. There is indefinite pain and weight in the epigastrium; there is flatulence; at times vomiting or diarrhea; and there may be loss of appetite or perversion of the appetite. There is a tendency to vertigo or even to fainting. There are cases in which there is a condition resembling typhoid, apparently due to ascaris. The intestinal catarrh may cause considerable diarrhea; and there are reports of numerous cases in which there is passage of stools containing mucus and blood, without tenesmus—that is, pseudodysentery—due to ascaris. There are cases in which a choleriform condition appears to be due to the presence of ascaris in the intestine—possibly due to some toxic action of the worm.

Nervous symptoms are very common, especially in debilitated and nervous persons and in children; and it is considered that these symptoms are due to the action of toxic products of the worms. There may be convulsions of different types; paralyses; pruritis, as of the nose and anus; pain in some part of the body; various psychic disturbances, as night terrors; disturbances of vision; loss of voice. A long list of nervous disturbances has been ascribed to the presence of ascaris in the intestine; and these disturbances disappear when the worms are expelled. How much of the disturbance is directly due to the worm and how much is psychic, from a knowledge of the presence of the worm, is difficult to say. However, serious nervous disturbances occur in young children, convulsions being fairly common. A pseudomeningitis is described, due to the action of the toxic products of the worm on the central nervous system.

There may be symptoms of pulmonary involvement; and Pantin says that in Fukien province, in China, cough is frequently seen in persons severely infested with ascaris, and that bronchitis is frequently cured by a vermifuge. It is probable that these symptoms are due to the action of the toxic products of the worms, and that they have no connection with the pulmonary lesions caused by the larval worms in their migration.

Montel has reported two cases of severe ascaris infection with contusion-like lesions of the skin over the head, arms, back and legs.

Diagnosis.—The diagnosis is made by finding the eggs in the feces, or by finding the worm in the feces or in the vomitus. Unfertilized eggs, long-oval in shape and more opaque than the fertilized eggs, may lead to confusion. At times the albuminous envelope may be torn off the egg; then the shell appears smooth and colorless. It is necessary to be on guard against mistaking various pollen grains and vegetable spores for the eggs of ascaris.

Patients with ascariasis may have fever with gastro-intestinal symptoms, and the febrile attacks tend to recur. It is necessary to examine the blood, in order to avoid confusion with *malaria* and *relapsing fever.*

The blood shows an eosinophilia. There may be anemia, usually secondary in type; but it may be of the pernicious type.

Complications.—Ascaris may pass through the wall of the intestine and produce peritonitis, at times forming a localized abscess which opens through the skin. One worm or a number of the worms may pass up the bile-ducts to the liver; and it is not uncommon to find the worms in a liver abscess or in the gall-bladder in cases of cholecystitis. The worm may at times pass up the pancreatic duct and cause pancreatitis. In the Army Medical Museum is a specimen in which an ascaris passed up the esophagus and into the trachea, causing suffocation.

Prophylaxis.—It is necessary to **avoid contaminated food and water; and food and water should be protected from dust and flies.** In some parts of China vegetables grown in ground that is fertilized with night-soil are considered to be an important source of infection. The **hands should be washed before eating**, to avoid carrying contaminated dirt to the mouth this is very important in children who play in the dirt.

Proper disposal of night-soil by the use of **properly constructed privies** is important in preventing infectious material from being scattered around; and advantage might be taken of Yoshida and Hotta's finding that the eggs do not develop in urine. If an attempt is made to disinfect the feces, it is necessary to choose some disinfectant—as **phenol**—that will penetrate the eggshell.

Treatment.—Oil of Chenopodium is especially good for the expulsion of ascaris. **After fasting and a purgative,** to remove the bulky food from the intestine so that the drug will come in contact with the worms, 2 to 10 drops of **oil of Chenopodium** is given on a lump of sugar, and is **followed** in an hour or two **by a dose of castor oil.** This treatment may be given every morning for not longer than three mornings. For a child five years old Gonzaga advises a single dose of 10 drops of oil of Chenopodium in 20 c.c. (5$\frac{3}{8}$ drams) of castor oil, after fasting. Darling and his co-workers found that, for the adult, the safest and best method of giving oil of Chenopodium was to give three doses of 0.5 c.c. (9 minims) with an interval of one hour between doses, after a day of soft diet and a milk breakfast on the day of treatment, the treatment being repeated in one week. They gave the drug in hard, dry gelatin capsules, filled a few hours before use.

It is important to give a dose of castor oil soon after the oil of Chenopodium, as the drug has a constipating action. If free catharsis does not result, the castor oil is to be repeated, to prevent the absorption of the drug as well as to carry the stupefied worms out of the intestine before they recover from the effects of the drug.

It must be remembered that oil of Chenopodium is toxic, and great care is necessary in giving it to poorly nourished or neurotic individuals or to persons with heart or kidney disease. Coutant reports a case of severe poisoning in a weak individual—a case of uncinariasis in a twenty-one year old man weighing ninety-five pounds—after the second dose of 0.6 c.c. (10 minims) of oil of Chenopodium, with a twenty-four hour interval between doses. Salant suggests that a **diet rich in fats and carbohydrates for a few days before administering the drug** may lessen the danger of toxic symptoms. Hall and Foster recommend that large doses of castor oil be given before and soon after the dose of oil of Chenopodium.

Santonin is satisfactory for the expulsion of ascaris. Deaderick advises, for a child under one year, 22 to 32 milligrams (1/3 to 1/2 grain); for a child one to five years, 65 to 130 milligrams (1 to 2 grains); for older children, 130 to 200 milligrams (2 to 3 grains). It is given with a dose of calomel, every morning or every other morning for three doses. When given in olive oil or castor oil, it seems to reach the worms and act on them more satisfactorily. It is to be remembered that santonin may cause yellow vision.

The feces should be examined for eggs one week after treatment, to determine whether all worms have been expelled.

Prognosis.—The prognosis is good in uncomplicated ascaris infection in the intestinal tract. The more severe nervous systems, as convulsions and paralyses, clear up promptly on removal of the worms. The liver conditions are more serious; and the cases of liver abscess have the same prognosis as liver abscess from other causes.

Pathogenic Action.—As in all worm infections, certain individuals may harbor numerous ascarides without any ill effects; on the other hand, some individuals present various symptoms from a rather small number of ascarides.

Ascaris lives in the contents of the small intestine; there is a difference of opinion as to whether or not the worm feeds on the substance of the intestinal mucosa and sucks blood. The buccal armature of the worm is such that it could readily attach itself to the mucosa and could produce lacerations that would enable it to feed on the mucosa and blood; and in man and lower animals harboring ascaris the intestinal mucosa often shows puncture-like lacerations. *Ascaris lumbricoides* is found free in the intestinal contents; but *Ascaris conocephala* is often firmly attached to the intestinal mucosa. The body fluid of ascaris contains oxyhemoglobin which probably comes from the blood of the host.

Extracts of ascaris are toxic for animals. Shimamutra and Fujii isolated a toxic substance from the body fluids of ascaris. This substance, when injected subcutaneously in horses, causes severe symptoms, as dyspnea, spasms, urticaria and edema; and large doses cause death. It is possible to immunize horses against some of the toxic extracts of ascaris. The fluid from the body cavity of the worm is irritating to the ocular and nasal mucous membranes. Goldschmidt found that persons apparently become sensitized in dissecting fresh ascaris. There are no symptoms during the first dissection; but subsequent dissections are followed by irritation of the ocular and respiratory mucosa, with asthmatic attacks. Injection of aqueous extracts of *Ascaris lumbricoides* produces eosinophilia, after sensitization. Some extracts of the worm will produce inflammation and necrosis of tissue; but, when the worm is found in abscesses, the abscess is due to bacterial infection carried in with the worm.

At times ascaris causes more or less severe anemia, and it is not clear whether this anemia is due to the absorption of toxic substances produced by the worm or to loss of blood from the worm feeding on the tissues of the host. Schwartz showed that the body fluid of *Ascaris lumbricoides,* taken from worms shortly after their removal from the host, is not hemolytic; but the body fluid taken from worms kept alive in salt solution for six or eight days is decidedly hemolytic. Schwartz suggests that the hemolytic substances in ascaris are of the nature of endotoxins. He also suggests that the toxic substances may be liberated only on the death of the worm, and that, as in the case of the fish tapeworm (*Dibothriocephalus latus*), anemia is caused by the absorption of toxic substances resulting from the death and disintegration of the worm.

It has been suggested that bacteria may enter the tissues through the wounds in the intestinal mucosa caused by the bites of the worms. It is also possible that bacteria may be introduced into the tissues through the wounds made by the larvæ in their migration after hatching from the eggs in the small intestine.

Ascaris larvæ, during their migration, cause considerable hemorrhage in the lungs; and experimental animals frequently die of pneumonia resulting from the invasion of the lungs by ascaris larvæ. Ransom points out that pneumonia, due to the invasion of the lungs by ascaris larvæ, is responsible for considerable loss among young pigs; and he suggests that invasion of the lungs by ascaris larvæ may cause pulmonary lesions in the human, citing experiments by Mosler and Lintz in which several children and an adult were affected with fever, difficulty in breathing, and bronchitis, a few days after swallowing ascaris eggs.

Ascaris may be found in the peritoneal cavity, without there being any lesion of the intestine; and it has been suggested that in such cases a young ascaris has penetrated the wall of the intestine and has developed in the peritoneal cavity as an erratic parasite. It is possible that in such cases there may be confusion with *Dioctophyme renale.* During its migration, the ascaris larva may get into the spleen or under the peritoneum; and it could well get into the peritoneal cavity.

At times, a large mass of worms may act as an obstruction in the intestine; and ascaris has been found in the intestine in strangulated hernia. Febrile conditions in the host increase the activity of ascaris, and cause it to wander from its normal habitat in the small intestine. Under such conditions, as well as under conditions which are not understood, ascaris may leave the small intestine. It may enter the stomach and be vomited, or may pass up the esophagus and enter the trachea or bronchi, the pharynx, the nasal cavities or the eustachian tube. It has even come out of the auditory canal when the tympanic membrane was ruptured; and it has passed from the nasal cavity, up the lacrimal duct, and appeared at the inner angle of the eye.

More commonly the worms pass into the large intestine and are passed in the feces; or they may enter the appendix, and give appendiceal colic.

At times the worms pass into the pancreatic duct or up the bile-duct; and ascaris has been found in liver abscesses. Aviles reports a case in which there were symptoms of gall-stones; and at operation a large ascaris was found partly obstructing the cystic duct.

When there are perforations, fistulæ, or abscesses, the worms may pass to the peritoneal cavity, the pleural cavity, the bladder, ureter, or uterus.

The presence of a mass of worms in the intestine produces a chronic irritation which causes an intestinal catarrh; and this is supposed to be the cause of the diarrhea that is sometimes met with in ascariasis.

Geographical Distribution.—The infection is found throughout the world, Iceland being the only country in which it is said not to be found. In the southern part of the United States it is second in frequency only to hookworm infection; and in Lucke's examination of 35,000 healthy white and colored soldiers in Kentucky, ascaris infection was more common than hookworm infection (3.76 per cent. infected with ascaris, and 3.27 per cent. infected with hookworms).

2. *Oxyuriasis*

Definition.—Oxyuriasis is the name given to the condition resulting from the development of *Oxyuris vermicularis* (pin-worm, seat-worm, thread-worm) in the intestine.

Etiology.—Predisposing Causes.—*Climate: Season.*—As it is not necessary for the egg to go through any period of development outside the body, and as there is no intermediate host, climatic or seasonal conditions have little effect on the occurrence of the infection. Conditions are more favorable for infection in warm and temperate regions, and Deaderick says that, in the southern part of the United States, more cases are observed in spring and summer than in other seasons.

Age.—The infection is found at all ages; but it is more common in children. Of 354 cases collected by Stiles and Garrison, over 86 per cent. were of children under fifteen years of age. The infection is more common in women than in men, probably because women are more exposed to infection in caring for the children.

Exciting Cause.—(*a*) *Morphology.*—*Oxyuris vermicularis* (Linnaeus, 1767) is white in color. The male is 2 to 5 millimeters (1/12 to 1/5 inch) long, with the blunt posterior end curved ventrally, and has one curved spicule 70 microns (1/360 inch) long. The female is 9 to 12 millimeters (3/8 to 1/2 inch) long; the tail is pointed; the anus is about 2 millimeters (1/12 inch) in front of the tip of the tail; the vulva is placed transversely a little in front of the junction of the anterior and second fourths of the body. *Oxyuris vermicularis* has a prismatic, longitudinal ridge on each side, which is characteristic.

(*b*) *Habitat.*—The earlier stages of the worm live in the small intestine; and the adults live in the large intestine. Young males and females are frequently found in the vermiform appendix. As far as is known, the various species of oxyuris found in lower animals are different from *Oxyuris vermicularis,* and do not infect man.

(*c*) *Evolution.*—The eggs are smooth, oblong, flattened on one side; the wall is thick; the egg is 50 to 54 microns (1/500 to 1/460 inch) long and 20 to 27 microns (1/1250 to 1/920 inch) in diameter, and contains an embryo at the time it is passed in the feces. As a result of this, it is possible to have auto-infection. The embryo will live a long time in the egg; but it does not stand exposure in water. When the egg is taken in by the new host the shell is digested off and the embryo is set free in the small intestine. The worms become sexually mature and copulate while still in the small intestine; they then pass to the large intestine to complete their development. Many of the males die and are passed out. The females pass toward the anus, and by their constant biting as they take in food, and by their constant movement, they produce marked pruritis. The worms, commonly the adult female full of eggs, are frequently found in the feces.

Epidemiology.—The female worms wander out of the anus and, as they cause considerable pruritis, the worm may be crushed in scratching. The eggs on the fingers may be carried to the mouth, and thus there is auto-infection. The eggs may get on the hands from soiled clothing or bedding; or they may be taken in with contaminated food. Vegetables grown on land fertilized with night-soil may carry the infection. Flies may play a part in the spread of the infection, as it is not necessary for the egg to go through any development outside the body.

Symptomatology.—A small number of worms may not attract attention, and the infection may die out. But the frequency of auto-infection leads to heavy infections; and various symptoms occur.

The intestinal symptoms are the most constant, the most persistent of which is pruritis ani, which is especially troublesome in the evening. This pruritis is due to the presence of the worms in the folds of the mucous membrane; and the mucous membrane is seen to be congested, and is studded over with small red points which are the result of repeated bites by the worms. The mucous membrane is covered with a layer of mucus, often blood-stained, which contains worms and their eggs. There is a catarrhal condition of the mucosa of the rectum; and it probably extends higher in the intestinal tract. There is loss of appetite, nausea, and vomiting, and the stools are often frequent, or there is actual diarrhea with mucus, at times blood-stained, in the stools.

As the worms are numerous about the head of the cecum, they are frequently found in considerable numbers in the vermiform appendix. The worms are not infrequently found in the appendix at operation for appendicitis, and it is agreed that they may cause appendicitis. Their presence in the appendix leads to a catarrhal condition of the mucosa, and the latter frequently shows hemorrhagic areas resulting from the bites of the worm. The worms in the appendix may irritate the mucosa and produce appendiceal colic. They may penetrate the mucosa of the appendix, and be found in the wall; and in this way they may carry bacterial infection into the wall of the appendix.

Oxyuris causes the same nervous symptoms as does ascaris, but much less frequently than ascaris. Convulsions may occur in children, and there may be melancholia or neurasthenia.

The irritation of the worms about the anus leads to reflex irritation of the genitalia, resulting in erotic sensations or in indefinite pain in the genitalia.

The worms may pass from the intestine to the stomach, and rarely up into the nasal fossa and the mouth. They may pass from the anus to the vagina and produce leukorrhea, with intense itching; they may even pass up into the uterus or into the tubes. The worms rarely enter the bladder. At times they may be found in abscesses and in subcutaneous inflammatory areas in the perineum; they may enter the wall of the small intestine and become encysted in the submucosa. The worms may reach the peritoneal cavity—whether through the intestinal wall or up through the vagina and fallopian tubes is not clear.

Diagnosis.—The worms are frequently found in the soft fecal matter, especially when the material is diluted and examined or is examined after a purgative. The worms or their eggs may be found in material scraped from the mucous membrane at the margin of the anus. At times the eggs are found by microscopical examination of the feces, especially of shreds of mucus on the surface of the fecal matter. As the female is not mature until she arrives at the lower part of the intestine, the eggs may not be found in the feces; and this fact must be borne in mind in examining for the presence of oxyuris. The blood shows a moderate eosinophilia.

Prophylaxis.—The worm lives a long time in the egg, and there is danger of infection from eating vegetables which have been fertilized with human excrement. The embryos do not stand exposure in water, so there is less danger from contaminated water. The infection may be transmitted by contaminated fruit. **The clothing and bedding of infected persons** is likely to contain the eggs in large numbers, and **should be sterilized.** A slight infection is very soon increased to a heavy infection through auto-infection. **The hands should be washed after defecation and before eating, and the nails should be cut short and kept clean.**

Treatment.—It must be remembered that only the gravid females are present in the lower part of the large intestine, and that the developing worms are in the small intestine and the upper part of the large intestine, and are constantly passing down toward the anus. This accounts for the frequent failure of enemata to cure the condition.

To expel the young worms from the small intestine, it is necessary to give some drug by mouth. **Oil of Chenopodium,** given as for ascaris, will remove the worms. It is to be remembered that oil of Chenopodium gives better results when **preceded and followed by a dose of castor oil;** and the toxic action of the drug must be kept in mind. **Santonin and calomel,** as advised for ascaris, will remove the worms. **Thymol,** in the dosage recommended by Ashford and King—for a child under five years, in size, 0.5 gram (7½ grains); five to ten years, in size, 1 gram (15.5 grains); ten to fifteen years, in size, 2 grams (30 grains); for an adult, 4 grams (62 grains)—will remove the worms. The usual precautions are to be taken in giving thymol. **Extract of quassia in castor oil** has been recommended. **Sulphur**—100 mgms. (1½ grains) to a child, 200 mgms. (3 grains) to an adult, three times a day—is recommended by Flynn.

To remove the adult female from the lower portion of the rectum, **enemata of infusion of quassia,** 30 grams (7¾ drams) of quassia chips to 500 c.c. (1 pint) of hot water, is the usual treatment. **Enemata of salt solution, salt and milk, and various other substances** are recommended. The enema is to be given with the buttocks elevated, and is to be retained for at least half an hour. The enema is given every evening for several evenings, then every second or third evening, until there is no more disturbance from the worms. This washing out of the gravid females relieves the irritation and lessens the danger of auto-infection.

To relieve the itching, **suppositories of one part of calomel or mercurial ointment in twenty parts of cocoa butter** are satisfactory.

Prognosis.—The prognosis is good.

Pathogenic Action.—Oxyuris lives in the intestinal contents and does not cause much injury to the host. The symptoms are due to irritation and slight injury of the intestinal mucosa by the worm. At times there are attacks of urticaria, which are probably due to toxic products from the worm.

Geographical Distribution.—The worm is found throughout the world.

(*b*) FAMILY STRONGYLIDÆ

This is an important family of worms, and it is divided into four *subfamilies:*

1. Strongylinæ
2. Trichostrongylinæ
3. Metastrongylinæ
4. Pseudalinæ (this subfamily does not interest us).

1. The Strongylinæ have a buccal capsule and are always parasites of the digestive tract. This subfamily is divided into *groups,* according to the structure of the caudal bursa in the male and the position of the vulva in the female, as follows:

A. Oesophagostomeæ. Two genera are of importance: Oesophagostomum and Ternidens.
B. Strongyleæ. One genus is of importance: Ancylostomum.
C. Bunostomeæ. Two genera are of importance: Bunostomum and Necator.

2. The Trichostrongylinæ have no buccal capsule, and are parasites of the intestinal tract. Three genera are of importance: Haemonchus; Nematodirus; and Trichostrongylus.

3. The Metastrongylinæ are parasites of the respiratory or circulatory apparatus. One genus, Metastrongylus, is of importance.

3. *Ancylostomiasis*

Ancylostomiasis, the condition due to worms of the genera Ancylostomum and Necator, is discussed under Hookworm Disease.

Oesophagostomum, Molin, 1861, lives in cysts in the submucosa of the large intestine. A number of species are parasitic in lower animals, and a few cases have been reported in man. *Oesophagostomum brumpti,* Railliet and Henry, 1905, *Oesophagostomum stephanostomum var. thomasi,* Railliet and Henry, 1909, and *Oesophagostomum sp.,* have been found in man. It is probable that monkeys are the normal hosts, and that the infections in man are accidental.

Ternidens, Railliet and Henry, 1909, is found in the large intestine of monkeys and man. *Ternidens deminutus* (Railliet and Henry, 1905) is the only species known.

Trichostrongylus, Looss, 1905, is found in the duodenum of the sheep. Three species, *Trichostrongylus instabilis* (Railliet, 1893), *Trichostrongylus probolum* (Railliet, 1896), and *Trichostrongylus vitrinus* (Looss, 1905), have been found in the small intestine of man. These worms are frequently red in color.

Mecistocirrus, Railliet and Henry, 1912, is found in the stomach of the pig and cow, and it may accidentally infect man. *Mecistocirrus fordi* (Daniels, 1908) has been reported from man.

Haemonchus, Stiles, 1903, lives in the stomach and duodenum of ruminants. One species, *Haemonchus contortus* (Rudolph, 1803), has been found in man. At least one case of severe anemia is charged to this worm. The development appears to be the same as for hookworms.

Physaloptera, Rudolphi, 1819, lives in the stomach of birds, reptiles, and mammals; it is rather common in monkeys. *Physaloptera caucasica,* von Linstow, 1903, and *Physaloptera mordens,* Leiper, 1908, have been found in the stomach of man.

(c) FAMILY TRICHOTRACHELIDÆ

In these worms, the anterior portion of the body is slender. Two genera are of importance: Trichuris and Trichinella.

4. *Trichuriasis*

Synonym.—Whip-worm disease; Trichocephaliasis.

Definition.—Trichuriasis is the condition resulting from the development of *Trichuris trichiura* (whip-worm) in the intestine.

Etiology.—PREDISPOSING CAUSES.—*Race.*—In Lucke's examination of 35,000 white and colored troops in Kentucky, infection with trichuris was third in frequency in worm infections, 1.52 per cent. of the white troops, and 0.06 per cent. of the colored being infected with trichuris. Of 523 cases collected by Stiles and Garrison, over 76 per cent. were children under fifteen years of age. Deaderick says that negroes are more commonly infected than whites; but in Lucke's examinations of healthy soldiers, 18 to 42 years of age, the infection was over twenty-five times as common in whites as in negroes, and Lucke considers that the difference is due to race.

Sanitary Arrangements.—Infection is more common in war and in moist regions, and in persons who live crowded together in towns and camps with poor sanitary arrangements. Lavergne found trichuris in 80 of 100 French soldiers in the trenches, and in 63 per cent. of the soldiers in cantonments behind the lines.

EXCITING CAUSE.—(*a*) *Morphology.*—*Trichuris trichiura* (Linnaeus, 1761), is white, or at times pinkish in color. The anterior two-thirds of the body is filiform and contains the esophagus; the posterior one-third is thicker and contains the intestine and the genital organs. The male is 30 to 45 millimeters (1 1/5 to 1 4/5 inch) long, with the posterior end blunt and curled up; there is one testicle; the genital opening is at the posterior end; and there is a single spicule, which is a formidable structure, 2.5 millimeters (1/10 inch) long, provided with a prepuce covered with spines. The female is 35 to 50 millimeters (1 2/5 to 2 inches) long; the posterior end is blunt and straight; there is one ovary, and the vulva is situated at the beginning of the thick part of the body.

(*b*) *Habitat.*—The worm lives in the cecum and in the vermiform appendix of man, rarely in the colon and in the small intestine.

The worm is attached by the slender anterior part of the body of the worm, being pushed through the superficial part of the epithelial cells of the mucosa.

Generally there are few worms—1 to 10—but there may be as many as 1,000. The females are present in far greater numbers than are the males. It is estimated that 3,000 eggs in a gram of feces corresponds to 900 worms; and when there are more than 10 worms there will be eggs in a cover-glass preparation of the feces.

(*c*) *Evolution.*—The eggs are elliptical or barrel-shaped, 50 to 55 microns (1/500 to 1/450 inch) long and 22 to 25 microns (1/1100 to 1/1000 inch) in diameter, with a thick brown shell having an opening at each pole closed by a plug of clear material. The egg contains a single cell when passed in the feces. Under favorable conditions of temperature, moisture, and oxygen supply, the embryo develops within the eggshell until it comes to be a coiled-up worm. This development requires six to twelve or even eighteen months, depending upon the conditions in the surrounding medium. Moist earth and water are the most favorable media for the development of the embryo.

The developed embryo, within the thick eggshell, will live as long as five years. It resists freezing for some time, drying, and putrefaction, and ordinary disinfectants penetrate the shell slowly.

Infection results from swallowing the eggs containing the fully developed embryos. The embryos escape from the eggshell in the small intestine, become attached to the mucosa in the head of the cecum, and develop into adult worms in about a month.

Epidemiology.—Infection results from taking in the developed eggs with contaminated food or water, as with ascaris infection. As a long time is necessary for development of the embryo in the egg, autoinfection is not possible; and it is not probable that flies play any important part in the spread of the infection.

Symptomatology.—Trichuris is the most frequent intestinal worm in many parts of the world; and it generally causes no symptoms. When the number of worms is large, there may be symptoms of varying severity.

DIGESTIVE DISTURBANCES.—When the worms are numerous, there may be diarrhea, with irregular, vague pains over the head of the colon; and cases are reported where there were numerous worms throughout the length of the colon, with passage of stools containing an abundance of mucus, and accompanied by tenesmus.

DISTURBANCES OF THE NERVOUS SYSTEM.—The disturbances may be the same as in ascariasis: convulsions, paralyses, vague pains in different parts of the body, night terrors, and disturbances of the special senses.

TRICHURIS ANEMIA.—In infection with trichuris there is at times a marked anemia of either the secondary or the pernicious type. The red-cells may be down to 600,000 per cubic millimeter. The patient is pale; and cardiac disturbances, as palpitation, anemic murmurs, and vertigo, are common.

Diagnosis.—The diagnosis is made by finding the eggs in the feces. There is a moderate eosinophilia; but there may be no eosinophilia when the anemia is severe or pernicious in type. Lavergne found no eosinophilia in his examinations of French soldiers.

Prophylaxis.—**Fecal matter should be disposed of** so as to prevent contamination of the soil. It is necessary to **avoid contaminated foods and water,** especially raw vegetables grown on ground fertilized or contaminated with human excrement. **Children and persons who work in the soil should be careful to wash the hands and clean the nails before eating and before putting the fingers into the mouth.**

Treatment.—Anthelmintics do not completely remove trichuris; but it is possible to reduce the number of worms so that no symptoms result from the few that remain. **Oil of Chenopodium,** given as for other intestinal worms, is the most satisfactory. **Thymol,** given as for hookworms, removes a large number of the worms. Montoya strongly recommends **fig tree juice**, in a single dose of 15 to 20 c.c. (4 to 5½ drams), followed in two hours by a dose of castor oil. **Enemata of solutions of benzin** have been recommended.

Prognosis.—In general, the condition causes no disturbance, or is benign. The severe forms of anemia have a more serious prognosis, as death may result from the anemia, especially from hemorrhage.

Pathogenic Action.—The worms are found in the head of the cecum, with the slender anterior part of the body of the worm thrust through the superficial part of the layer of epithelial cells of the mucosa, the head end of the worm being thrust through, so as to lie free in the intestinal cavity. The worms feed on the intestinal contents and not on the tissues.

The worms attached to the mucosa of the intestine ordinarily cause no disturbance; but at times they may penetrate the mucosa or even the muscular coat, and open the way for entrance of bacteria. Trichuris has been accused of introducing various disease-producing organisms, as *Bacillus typhosus, Spirillum choleræ asiaticæ,* and *Bacillus dysenteriæ;* but it is probable that the worm plays no part in the introduction of these organisms. It is frequently found in the vermiform appendix, and has been accused of causing appendicitis. Montoya says that it is a common cause of chronic dysenteriform diarrhea in Colombia.

The worm excretes products which are toxic for the host; and, when the worms are numerous, there may be severe secondary anemia; or the blood-picture may be that of pernicious anemia.

Trichuris trichiura is found in monkeys, and monkeys also harbor other species of trichuris. Many of the lower animals harbor trichuris; *Trichuris depressiusculus* is common in dogs; *Trichuris nodosus* is found in mice; *Trichuris unguiculatus* in rabbits; *Trichuris affinis* in sheep; and *Trichuris crenatus* in pigs.

A severe anemia, due to trichuris, is well known to veterinarians in some parts of the world.

Geographical Distribution.—The infection is found throughout the world, the worms being found in the stools of from 5 to 85 per cent. of the people in different regions.

5. *Trichiniasis*

Synonym.—Trichinosis.

Definition.—An acute condition, caused by *Trichinella spiralis,* and characterized by remittent fever, edema of the face, pain and soreness in the muscles, and emaciation. Anatomically the larval worms are found in the muscles.

Etiology.—(*a*) *Morphology.*—*Trichinella spiralis* (Owen, 1835)* is the cause of the disease. The adults live in the upper part of the small intestine; the embryos pass by the lymph and blood stream to the striated muscles; and the encysted larvæ live in the striated muscles.

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* Meigen had given the name Trichina to a genus in the Diptera, in 1830; so it was not available as a name for this organism. In 1895, Railliet changed Owens' genus name to Trichinella.

The adult worms are white in color; the anterior end is small, and the body enlarges progressively toward the posterior end. The male is 1.4 to 1.6 millimeters (1/18 to 1/16 inch) long, and 40 microns (1/625 inch) in diameter, has two conical appendages at the caudal end, and two pairs of papillæ behind the cloacal opening which is between the two caudal appendages. The female is 2 to 3.5 millimeters (1/12 to 1/7 inch) long, and 60 microns (1/416 inch) in diameter. The vulva is in the anterior fifth of the body, and the worm is viviparous.

(*b*) *Evolution.*—When trichinous meat is eaten, the cyst-wall is digested in the stomach and the worms are liberated, and pass actively to the small intestine where they grow to maturity in two or three days. The females are fertilized by the end of the third day, the eggs being about 20 microns (1/1250 inch) in diameter, and containing an embryo which escapes from the egg in the cavity of the uterus. On the sixth or seventh day the fertilized females burrow with the anterior end into the mucosa of the intestine, so that at least the anterior fifth of the worm is in the tissues, and the embryos, escaping from the vulva, will be in the tissues. Some of the worms go deep into the intestinal wall and may even get to the mesentery or the mesenteric glands.

The female continues to give birth to embryos for about six weeks; but most of the embryos are passed in the first two weeks; one female may give birth to 1,500 embryos. The embryo when born is 90 to 100 microns (1/280 to 1/250 inch) long, and 6 microns (1/4000 inch) in diameter, and tapers slightly from the posterior to the anterior end. The embryos are passed directly into the lymph-spaces of the mucosa and submucosa. There is a difference of opinion as to how the embryos get from the intestinal wall to the muscles; but it is probable that they pass from the intestinal wall with the lymph, to the thoracic duct, and to the right heart. Possibly some of them go from the intestine to the right heart by way of the portal vein. As the embryos are smaller in diameter than a red blood-cell, they pass through the lung capillaries into the general circulation, and to the striated muscle, where, partly mechanically but mainly as the result of a chemotactic action, they leave the capillaries and penetrate actively between or into the muscle fibers.

As early as the ninth or tenth day the embryos are found in fair numbers in the muscles. The embryo grows rapidly in the muscle, completing its development in the muscle in about fifteen days, and becoming as much as 1 mm. (1/25 inch) in length; then it coils up and encysts. Encystment begins about one month after infection; the cyst-wall is distinct by the end of the fifth or sixth week; and encystment is complete by the end of the eighth to twelfth week. The embryos in the cysts are differentiated into male and female; and they live twenty to thirty years in these cysts. When the meat containing these cysts is eaten, the cyst-wall is digested, the worms are liberated, and the cycle is started over again.

(*c*) *Resistance.*—While the encysted worms are quite resistant to cold, most of the findings of great resistance are due to failure to recognize the long time it takes to heat or cool a mass of meat.

Perroncito has shown that the encysted trichina larva is killed in five to ten minutes at 48°–50° C. (118.4°–122° F.); and Ransom has shown that it is quickly killed at 53°–55° C. (127.4°–131° F.).

Ransom has shown that a large proportion of encysted trichinæ, after exposure for fifteen days at — 10.9° C. (12° F.), are more or less active when examined on a warm stage; but they rarely produce infection when fed to experimental animals, and the infection when produced is slight. After exposure for fifteen days at — 17.8° C. (0° F.), the encysted trichinæ are practically never active when examined on a warm stage; and they never produce infection when fed to experimental animals.

Salt and antiseptics penetrate the capsule slowly, especially after it is calcified; and the resistance of the worm to these substances is dependent upon the impermeability of the capsule.

(*d*) *Occurrence in Lower Animals.*—The infection is common in hogs throughout the world. Ransom tabulated the results of the United States Government trichina inspection of over eight million hogs exported during the nine years, 1898 to 1906. Of these, 1.41 per cent. contained living trichinæ, and in addition 1.16 per cent. contained dead trichinæ and trichina-like bodies.

In Germany, the proportion of infection among hogs was 5.5 per 10,000 in 1885, and had been reduced to 1.4 per 10,000 in 1899. The proportion of infection varies in different parts of Germany: thus, in 1896, it was 2.1 per 10,000 in all of Prussia, and 27.2 per 10,000 in Posen; in 1906, it was 0.5 per 10,000 in all of Prussia, and 6.1 per 10,000 in Posen.

The infection is not uncommon in hogs in Russia, Sweden, Holland, and Denmark. It is present in Australia, India, China, Egypt, Algeria, Mexico, Argentina, and Chile. It is rare in France, Italy, and Switzerland.

The infection occurs in the wild boar; and Wortabet reports an outbreak of the disease in Syria, as a result of eating the flesh of the wild boar.

Black, common, and sewer rats are commonly infected. Dogs are quite commonly infected in some parts of Europe, though dogs are not easily infected experimentally. Cats are rarely infected. The infection has been found in the mouse, fox, bear, and badger.

Experimentally, guinea pigs and rabbits are readily infected. Cattle, sheep, and horses are difficult to infect; and usually there is only development of the adult worms in the intestine, with little or no development of the embryos in the muscles. A number of lower animals can be infected. The worms develop to adults in the intestine of some birds, as pigeon, goose, chicken, and grouse; but there is no development of the larvæ in the muscles.

Lower animals are the normal hosts for trichina; infection in man is in the nature of an accident. It is readily seen that the embryo worms encysted in the muscles of man have little chance of further development; only among lower animals are conditions suitable for the development of the worm from generation to generation. There is doubt as to whether the hog or the rat is the normal host for trichina. Different investigators in Germany have found 5.3 to 22.1 per cent. of the rats infected with trichina; but in these examinations the trichinous rats were caught in slaughter houses and where they had opportunity to eat trichinous pork. In slaughter houses, as much as 50 per cent. of the rats were trichinous. Billings found all rats from a slaughter house in Boston trichinous. From these considerations, Stäubli is of the opinion that the hog is the normal host of trichina, though he considers that rats may play a part in keeping the infection going in hogs—through the eating of infected rats by the hogs.

Epidemiology.—Trichiniasis in man results from eating raw or imperfectly cooked pork containing living, encysted trichinæ.

One outbreak in the United States was traced to infected beef; but as it is difficult to infect cattle experimentally, and as infection might result only when cattle were fed on garbage containing raw pork scraps, for practical purposes, pork is the source of infection.

Ransom found more or less definite statements regarding the pork causing about 1,200 of the United States cases. Raw sausage was the cause of 225 cases; raw ham 213 cases; sausage 141 cases; raw or incompletely cooked pork 340 cases.

In the United States, local outbreaks of the disease, when due to eating sausage, are usually traceable to a small slaughter house, to a community, or to the slaughtering of one or several hogs by a family for its own consumption. Under such conditions, if a hog is trichinous, the persons eating the meat get a large dose of infectious material. On the other hand, if a large slaughter house gets a trichinous hog in with other hogs, the trichinous meat is mixed with meat from many other hogs, and no person receives a large dose of infectious material, and there are no symptoms.

Symptomatology.—When the infection is slight, there may be no symptoms, or the symptoms may be slight and indefinite. When the infection is severe there is an acute febrile condition which is fairly well characterized, and which is conveniently described in three stages, corresponding to the stages in the development of the worm.

(1) STAGE OF INTESTINAL INFESTATION.—The symptoms may set in a few hours after eating the trichinous meat, with heaviness in the epigastrium, nausea and vomiting, mild diarrhea, and pain and cramps in the abdomen. The diarrhea becomes more severe, until the stools are watery, or they contain bloody mucus. At times there is constipation. The temperature gradually rises until, at the end of the first week, it is 39.2° to 40° C. (102.4° to 104° F.). There is great prostration from the beginning, with pain and stiffness in the muscles, and muscular twitching.

The early symptoms may be so severe that the patient dies in twenty-four to forty-eight hours after eating the trichinous meat; or there may be no symptoms until from seven to nine days after eating the meat.

(2) STAGE OF DISSEMINATION.—By the end of the first week the embryos are passing through the intestinal mucosa and invading the lymph and blood stream. A mild edema of the face, especially of the eyelids, is a striking symptom at this time; and this edema may be the first symptom. The temperature continues high, with a morning remission. Profuse sweats are frequent. There are severe rheumatoid pains in the muscles and the limbs are flexed, partly as a result of contractures of the muscles. The muscles are swollen and are stiff, hard and tender: those of mastication, deglutition, and respiration are especially affected, with disturbance in their function. The eye-muscles are affected so that movement of the eyes is painful. Subconjunctival hemorrhages are common and are frequently bilateral. There may be nosebleed.

Bronchitis is a constant symptom; and frequently there are attacks of asthma or dyspnea. The patient is greatly prostrated and is dull and apathetic: there may be delirium. The tendon reflexes are commonly lost.

The urine is decreased in amount, contains albumin, hyaline and granular casts, and gives a marked diazo-reaction.

(3) STAGE OF ENCYSTMENT.—About the end of the fourth week the embryos begin to encyst in the muscles, and about the end of the sixth week enough of the embryos have encysted so that the symptoms begin to lessen. The temperature returns to normal and the disturbances in the muscles subside. The patient is extremely emaciated and anemic. There is often marked edema of the face, with less marked edema of the abdomen and the extremities. There may be a miliary eruption, and pruritis is not uncommon.

When recovery takes place, the edema disappears and the patient passes through a long convalescence. Muscular weakness persists for several months or longer, and the muscles may remain painful and tender for a year or more.

Diagnosis.—CLINICAL DIAGNOSIS.—A clinical condition of gastro-intestinal disturbance, followed by a typhoid-like condition, with edema of the face—and especially of the eyelids—with pain, hardness, rigidity and contractures of the muscles and loss of the tendon reflexes, should lead one to suspect trichiniasis. A history of the patient's habits in regard to the eating of insufficiently cooked pork, and especially a history of recent eating of such pork, is important. There may be a history of a number of persons eating the same pork and being affected in the same way.

The disease resembles *typhoid fever* and is often mistaken for it. The spleen is not enlarged in trichiniasis.

The disease may be mistaken for *chronic rheumatism;* and in some cases of chronic rheumatism, laboratory examination of a piece of muscle has shown the presence of trichinæ.

Laboratory Diagnosis.—It has been suggested that if the disease is suspected early, the adult worms—especially males—may be found in the stools. But it is very rarely possible to find the adult worms in the stools at any time; no importance can be attached to failure to find them.

The embryos are present in the peripheral blood during the stage of dissemination; and there are reports of a number of cases in which the embryos were demonstrated in the peripheral blood. In experimental animals, as rats, the embryos are present in the peripheral blood as early as the seventh day and as late as the twenty-seventh day after infection, being most numerous from the eighth to the twenty-fifth day.

The embryos may be found in the blood on direct examination, or by drawing 5 to 10 c.c. of blood from a vein and putting it in 100 c.c. of 3 per cent. acetic acid solution, centrifuging, and examining the sediment.

The embryos may be found in the cerebrospinal fluid, and Lintz thinks that examination of the cerebrospinal fluid may be an aid in diagnosis. Lintz found the embryos in the cerebrospinal fluid twenty-one days after the patient had eaten trichinous meat: the clear fluid was centrifuged and the sediment examined. Elliott found the embryos in the cerebrospinal fluid when they were not found in the muscles. Salzer found the embryos in the cerebrospinal fluid nearly as frequently as in the blood—in the cerebrospinal fluid of 8 out of 14 cases, and in the blood of 9 out of 14 cases. Cummins and Carson found one embryo in the cerebrospinal fluid of 1 out of 12 cases; they found embryos in the muscles of 8 out of 9 cases, and they are doubtful of the value of examination of the cerebrespinal fluid as a routine method of diagnosis. It appears that examination of the cerebrospinal fluid is of diagnostic value during the Stage of Dissemination—at the same time at which the embryos are found in the peripheral blood.

By the fifth or sixth week the encysted embryos can be found by snipping out a piece of muscle and examining it.

The blood shows an eosinophilia of 15 to 30 per cent. or higher; but there may be marked fluctuations in the eosinophil percentage from day to day; and there may be no eosinophilia when there is secondary bacterial infection. The eosinophilia may persist for months. There is a leukocytosis of from 25,000 to 30,000 per cubic millimeter.

Prophylaxis.—Prophylaxis consists in **preventing the eating of pork which contains living trichina larvæ**; and this is carried out (1) by **preventing the infection in hogs**; (2) by **preventing pork which contains living trichinæ from getting into the market**, and (3) by the **thorough cooking of all pork.**

(1) Hogs become infected through eating scraps of trichinous pork, or through eating trichinous rats. Hogs should not be fed on slaughter house waste; and pork scraps should not be fed to hogs or put in garbage that is fed to hogs. Rats and mice should be exterminated in hog pens; and dead hogs, rats, and mice should be disposed of in such a manner that hogs will not have an opportunity to eat them.

There is no danger from infection through feces of rats, mice, and hogs, as the trichinæ passed out in the feces do not cause infection when swallowed again.

(2) On first thought, it would seem that a trichina inspection of all pork would prevent trichinous pork from getting into the market. But practical considerations and experience lead to the conclusion that such inspection is not practical and cannot be depended upon. The United States has no trichina inspection, though, in order to meet the requirements of certain countries regarding importation of pork, there was formerly a trichina inspection of pork intended for export.

The inspection must be microscopic; and Ransom says it would cost five million dollars a year to carry out the inspection. Even if carried out, the inspection would not prevent trichinous meat from getting into the market, as the encysted larvæ are very frequently missed. Thus, Germany has had an elaborate system of trichina inspection of pork; but Stiles and Hassall showed that of 6,329 cases of trichiniasis, with 318 deaths, in Germany from 1881 to 1898, 2,042 cases and 112 deaths were from meat that had been examined and released for trade as free from trichina.

But in this country, according to Ransom, 40 per cent. of the slaughtered animals do not receive federal inspection; and no system of inspection would cover the killing of a hog by a family for its own consumption or in a small community.

These considerations have led the Bureau of Animal Industry, of the Department of Agriculture, to find some method, other than inspection, for preventing trichinous pork from getting into the trade. Ransom has carried out an extensive investigation of the action of heat and refrigeration in the destruction of trichinæ in meat; and he has also done some work on the action of salt, smoking, and other methods of preserving meat.

On the basis of the results of these investigations, the federal meat inspection authorities have adopted a requirement that all muscle tissue of pork, which is to be used in the preparation of products to be eaten raw, must be held for twenty days at a temperature not above —15° C. (5° F.), or it must be heated to a sufficiently high temperature—about 60° C. (140° F.)—to insure the killing of all trichinæ.

While a great deal of the American pork imported into Germany was found to contain trichinæ, it was frequently noted that the worms were dead; and this was probably due to the refrigeration rather than to drying, as suggested by Ostertag.

An important consideration in refrigeration is the length of time required for the center of a mass of meat to reach the temperature of the refrigerator. Ransom found that it takes about a week for the center of a barrel of meat, originally at a temperature of 0° C. (32° F.) to reach a temperature of —15° C. (5° F.) when placed in a refrigerator at —15° C. (5° F.).

The investigations of the action of salt and curing processes on trichinæ have not reached a stage where any definite results have been announced. It is probable that these processes would kill the trichinæ in the superficial part of the meat only, and could not be depended upon.

(3) Thorough cooking of all pork is the important method of prophylaxis that can be carried out by the individual; all persons should be educated as to the danger of eating raw or insufficiently cooked pork.

An important consideration in cooking meat is the length of time required for the center of a piece of meat to reach a temperature high enough to kill trichinæ. Ransom found that in cooking a 15 pound ham in water maintained at a temperature of 82.2° to 85° C. (180° to 185° F.), it required two and one-half hours to raise the temperature of the center of the ham from 25.6° to 58.3° C. (78° to 137° F.); and it required three and one-half hours to raise the temperature of the center of the ham from 7.8° to 58.3° C. (46° to 137° F.). A ham of the same size required five hours' cooking in water at a temperature of 71.1° to 73.9° C. (160° to 165° F.) to raise the temperature of the center of the ham from 25.6° C. to 58.3° C. (78° F. to 137° F.). An ordinary frankfurter sausage requires ten minutes' cooking in water at 71.1° C. (160° F.) to raise the temperature of the center of the sausage from 25.6° C. to 58.3° C. (78° F. to 137° F.). From a consideration of the length of time it takes for heat to penetrate meat, it is evident that meat supposed to be thoroughly cooked, is often insufficiently cooked to kill trichinæ.

Treatment.—Generally the treatment must be entirely symptomatic and supportive.

If the patient is seen soon after eating the meat, it may be possible to get rid of a number of the worms by **washing out the stomach,** giving a cathartic, such as **calomel,** and by giving **thymol** in the usual way. Merkel advised alcohol in the form of **brandy,** in large doses.

Booth and his co-workers report good results in the treatment of a case with **thymol dissolved in sterile olive oil** (65 mgms. [1 grain] of thymol in 1 c.c. of oil), giving 2 to 3 c.c. subcutaneously or intramuscularly every day for seven days.

The **arsenicals,** as salvarsan, **have no action on trichinæ.**

Salzer reported that **serum of animals convalescent from trichiniasis** had prophylactic and curative action; but Schwartz's investigations did not bear out this finding.

Prognosis.—The mortality of trichiniasis is difficult to determine, as mild cases do not apply for treatment and are not reported. In Ransom's tabulation of about 320 cases in the United States during the five years, 1909-1914, there were 19 deaths—a mortality of about 6 per cent.—while in his tabulation of all reported cases—about 1,550—in the United States, there were 270 deaths—a mortality of about 16 per cent. In 6,329 cases in Germany from 1881 to 1898, there were 318 deaths—a mortality of slightly over 5 per cent. In the Hedersleben epidemic in Germany, in 1865, in a population of 2,000 persons, there were 337 cases and 101 deaths.

The disease is generally mild in children.

It is generally held that the disease is milder in cases having severe diarrhea in the early days of the infection.

Mechanism of the Disease Process.—The adult worms produce their effects in the intestine, while the embryos produce their effects in the muscles. When a large amount of trichinous pork is eaten there is an intense catarrhal inflammation of the entire intestinal tract, and there may be considerable hemorrhage into the intestinal canal. This inflammation is not as severe in man as in lower animals, probably because man does not get so large a dose of infectious material. The inflammation is due to mechanical irritation and probably also to toxic products from the worms.

It is generally stated that the adult worms die—the males soon after copulation, and the females in six or seven weeks—and are passed out with the feces of the host or are digested as they pass down the intestinal canal. But even with the most careful search it is rarely possible to find the adult worm in the feces. Stäubli showed that the adult worms are not digested, as he fed living adult trichinæ to rats; the worms appeared in the feces, well-preserved but dead. From this, Stäubli is of the opinion that the adult worms die in the intestinal wall and are passed out with the feces from time to time, the difficulty in finding the worms in the feces being accounted for by the fact that there are very few worms in the feces at one time, the process of elimination extending over a long period. Bloch found numerous worms in the feces, after giving the patient a dose of calomel. Sulzer found worms in the stools of all of his patients, and he infected two dogs by feeding them the stools of patients.

By the seventh day the embryos are passing into the lymphatics, and through the general circulation to the muscles; and it is during their migration into, and their development in, the muscles that the severe typhoid-like symptoms occur. The embryos are most numerous in the most used muscles, as they have the richest blood supply—as the diaphragm, intercostal muscles, the muscles of the neck, larynx, tongue, and eyes. In the long muscles they accumulate toward the tendinous portion of the muscle. In severe infections the embryos are found in the heart-muscle, in the wall of the intestine, and in practically any tissues; but they do not complete their development or encyst in any tissue except striated muscle, and they do not complete their development or encyst in the heart-muscle. It is not probable that the embryos move actively through the tissues to any extent though Brumpt is of the opinion that they pass through the wall of the intestine to the peritoneal cavity, and he has found numerous embryos in the peritoneal cavity. They are also found in the pleural and pericardial cavities. They are found in the cerebrospinal fluid; and they may be numerous in the milk of a nursing woman. They are not found in the urine.

There is difference of opinion as to whether the embryo penetrates the muscle-fiber or develops in the connective tissue between the muscle-fiber, also as to how the cyst-wall is formed. Some authorities hold that the embryos develop in the connective tissue between the muscle-fibers and that the irritation causes proliferation of the fixed tissue-cells, forming a granular and cellular capsule about the worm, the capsule later becoming fibrous tissue. Other authorities hold that the embryo enters the muscle-fiber and develops there, and that the outer layer of the cyst-wall is formed by the sarcolemma of the infected muscle-fiber, and that the inner part of the cyst-wall is formed from the granular material resulting from the degeneration of the muscle-fiber.

It is probable that both opinions are partly right, and that the embryo enters the muscle-fiber, and that the capsule is formed from the connective tissue between the muscle-fibers. The infected muscle-fiber degenerates, and there is degeneration of the neighboring fibers. The connective tissue between the muscle-fibers proliferates and forms the capsule or cyst-wall; and a fairly rich network of blood capillaries forms over the surface of the cyst, and masses of fat form at the poles of the cyst. Calcification of the cyst-wall begins, first at the poles, in six months to two years, and is complete in eighteen months to three years. The larva remains alive for as much as thirty years in the calcified capsule; but finally the larva dies and becomes calcified, or at times the larva and the cyst-wall are absorbed.

The severity of the symptoms depends upon the amount of infectious material ingested; the symptoms are due to toxic products of the worms, and to toxic substances resulting from the breaking down of the muscle-tissue.

Flury considers that the vomiting, diarrhea and abdominal pain, which come on soon after eating trichinous meat, are due to toxic substances (fatty acids, lactic acid and purin derivatives) in trichinous meat; and that some of these substances are products of the worm itself. He also finds in trichinous muscle a heat-resisting toxic substance, which he considers is a product of the worm. This toxin has a special action on the walls of the capillaries; and he considers that the hemorrhages, the bronchitis, and the attacks of asthma and sudden dyspnea are due to this toxin.

Flury found that the glycogen of the muscle becomes greatly reduced as the trichina embryo becomes very rich in glycogen. The breaking down of the muscle tissue results in the formation of nucleoproteids, purin derivatives, creatin, guanidin derivatives, volatile acids and lactic acid. These decomposition products cause the fever, prostration, the pains and hard infiltration in the muscles, and the nervous symptoms. It is probable that the eosinophilia is due to these decomposition products—especially the nucleoproteids and purins—though products of the worm may play some part in the production of the eosinophilia. The fatty change in the liver and the changes in the renal epithelium are probably due to these decomposition products.

The late edema is due to the renal disturbance and to cachexia. But there has always been difficulty in explaining the early edema. Flury is of the opinion that the early edema is due to a combination of nucleoproteid-like substances from the destruction of the muscles, acid formation, hydremia and disturbance of water and mineral metabolism, and the toxic changes in the capillary walls.

IMMUNITY.—There is no immunity following an attack of the disease. Schwartz found no evidence of immune substances in the serum of experimentally infected animals.

COURSE OF THE DISEASE: CAUSE OF DEATH.—Mild cases last two or three weeks; severe cases last from six weeks to three or four months.

Death rarely results from the intestinal disturbance in the first couple of days of the infection. Death rarely occurs before the second week or after the seventh week, and is due to exhaustion during the fever, to cachexia, or to pulmonary complications, as bronchopneumonia.

Pathology.—MACROSCOPIC.—When the patient dies about the fourth week, there is emaciation, edema, and effusion into the serous cavities. The intestine and adjacent mesentery are congested, and there are congestion and ecchymoses in the intestinal mucosa. The intestinal contents may consist of blood-stained mucus. The mesenteric glands are swollen. There may be small hemorrhages in the lungs; and there may be areas of lobular consolidation. The liver may be intensely fatty; the spleen is little or not at all enlarged. The meninges and brain are congested and may show minute hemorrhages. The other organs show no change.

The recently encysted embryos in the muscles are not visible to the naked eye; but after calcification they are visible as minute white specks. In Williams' series the encysted embryos were visible to the naked eye in 2 cases, though they were found microscopically in 27 cases.

Subconjunctival hemorrhages, about the cornea, are very frequent. Furuncles, due to secondary bacterial infection, are quite frequently present.

MICROSCOPIC.—The intestinal mucosa is swollen, and the epithelium eroded. There may be collections of polymorphonuclear leukocytes, but there is no local eosinophilia.

Early in the disease the liver shows no change, but later there is marked fatty degeneration. The kidney epithelium shows cloudy swelling; and there are albumin and hyaline and granular casts in the urine. Late in the disease there may be sugar in the urine.

The hemorrhagic foci in the lungs may contain embryos; and this has led to the belief that the hemorrhages were due to plugging of the capillaries by embryos; but Flury considers that the hemorrhages are due to the action of a heat-resisting toxic substance which is present in trichinous muscle.

There are collections of mononuclear round-cells about any worms there may be in the heart-muscle, liver, pancreas and brain; and round-cells collect in the hemorrhagic areas in the brain and meninges. There are also collections of lymphocytes and eosinophils in the heart-muscle.

The important microscopic finding is the encysted embryos in the muscle, the thin capsule about the coiled-up worm being visible when the patient dies five or six weeks after infection.

The fully developed cysts are lemon-shaped, the shape varying in different animals—being elongate in man and the hog, and more oval in the rat—the long axis of the cyst being in the long axis of the muscle-fiber. In man the cysts are 200 to 500 microns (1/125 to 1/50 inch)—usually about 400 microns (1/60 inch)—long; and 100 to 300 microns (1/250 to 1/80 inch)—usually about 250 microns (1/100 inch)—in diameter. Usually the cyst contains a single worm, but it may contain two or more.

Early in the disease the blood shows a marked increase in the number of red-cells and a moderate increase in the percentage of hemoglobin. Stäubli thinks this is a relative increase, due to thickening of the blood. Later there is a marked anemia, the red-cells going as low as 2,500,000 per cubic millimeter, and the hemoglobin falling as low as 45 per cent. There is a leukocytosis, the leukocytes going as high as 25,000 to 30,000 per cubic millimeter. While the infection consists only of adult worms in the intestine, there is no change in the eosinophils; but, with the invasion of the tissues by the embryos, the eosinophils increase to 15 to 30 per cent. or even to 68 per cent. of the total number of leukocytes.

Secondary bacterial infection is common; and streptococci and staphylococci have been isolated from the blood of cases. Stäubli thinks that the bacteria enter the tissues with the worms from the intestine. There is frequently bronchitis; and areas of bronchopneumonia are not uncommon.

History.—Encysted trichinæ were observed in the muscles of man by Tiedemann in 1822; and in 1828 Peacock described them as "little bodies." In 1832, Hilton suggested that they were parasites; and in 1835 Paget recognized that they belonged to the nematodes. Paget sent some muscle tissue of an Italian to Owen; and, as the slender worms were spirally coiled up, Owen gave the name *Trichina spiralis* to the parasite. Bischoff held that the parasites appeared in the muscles as a result of spontaneous generation; but von Seibold, in 1844, and Dujardin, in 1845, held that the worms in the muscles were the young form of some unknown nematode.

Up to this time the parasite was known only in the muscles of man; but in 1845 Herbst found them in a cat, and in 1847 Leidy found them in hogs. During the next few years a great deal of work was done on the life cycle of the worm; and the muscle forms were taken for the larva of various worms, including *Trichuris trichiura.* Leuckart and Virchow observed the development of sexually mature worms in the intestine of mice and dogs fed on trichinous meat; but they thought the adults were either Trichuris or Strongylus. Later, Virchow recognized that it was a new worm, and described the life cycle as now known.

In 1860, Zenker recognized the worm as the cause of a severe febrile disease, and showed that the disease in man was connected with eating trichinous pork. During the next few years a number of outbreaks of the disease were reported, and since that time the disease has been given considerable study. In 1897, Thayer and Brown noted the marked eosinophilia that occurs in the blood during the disease.

Geographical Distribution.—The disease is found throughout the world; but, as it results from eating insufficiently cooked pork, it is more common in some countries than in others.

It is difficult to determine the prevalence of the disease in human beings, as many mild cases do not receive medical attention, and some cases are not diagnosed or are not reported. Ransom gives a tabulation of 1,558 cases of trichiniasis in the United States from 1842 to 1914. All parts of the country are represented, New York leading with 355 cases and Pennsylvania next with 261 cases. There were 6,329 cases in Germany from 1881 to 1898.

In postmortem examinations throughout the civilized world, encysted trichinæ are found in the muscles of 0.5 per cent. to 2 per cent. of the bodies. Osler found trichinæ in 0.6 per cent. of 1,000 post-mortem examinations at Baltimore and elsewhere; while Williams, who made a special search for trichinæ, found them in 5.34 per cent. of 505 postmortem examinations in Baltimore, Philadelphia, Detroit, and Denver. None of Williams' patients died of trichiniasis.

Gnathostomum, Owen, 1836, lives in the stomach of various mammals, attached to the mucosa, and later in cysts in the submucosa. In these worms, the anterior part of the body, or the entire body, is covered with chitinous lamellæ; the posterior border of each lamella bears several spines, giving the worm the appearance of being covered with spines. *Gnathostomum spinigerum* (Owen, 1836) is found in the stomach of carnivorous animals, and has been found as an erratic parasite in subcutaneous cysts in man.

Rhabditis, Dujardin, 1843, generally lives free in decomposing material. *Rhabditis niellyi* (R. Blanchard, 1888) has been found in papules on the skin of man.

(*d*) FAMILY ANGIOSTOMIDÆ

The angiostomidæ are small worms, having two generations: a free-living sexual generation, and a parasitic hermaphrodite or parthenogenetic female generation.

6. *Strongyloidiasis*

Synonyms.—Strongyloidosis; Anguilluliasis; Anguillulosis.

Definition.—Strongyloidiasis is the condition resulting from infection with *Strongyloides stercoralis.*

Etiology.—Exciting Cause.—(*a*) *Morphology of the Organism.*—*Strongyloides stercoralis* (Bavay, 1877) is the cause of the condition. There are two generations in the cycle of development of the worm: (1) the parasitic generation, consisting of parthenogenetic females; (2) the free-living generation, consisting of males and females.

The parasitic female is 2.2 to 3 millimeters (1/11 to 1/8 inch) long, and 34 to 70 microns (1/735 to 1/360 inch) in diameter. The vulva is in the posterior third of the body; the uterus contains 5 to 9 eggs, 50 to 58 microns (1/500 to 1/430 inch) by 30 to 34 microns (1/835 to 1/735 inch).

In the free-living form the male is 0.7 millimeter (1/35 inch) long, and 35 microns (1/700 inch) in diameter; the tail is curved ventrally; there are two curved spicules, 38 microns (1/660 inch) long; and several pre-anal papillæ. The female is 1 millimeter (1/25 inch) long, and 50 microns (1/500 inch) in diameter; the vulva is a little back of the middle of the body; the eggs are 70 microns (1/360 inch) by 45 microns (1/630 inch) in size.

(*b*) *Evolution.*—The eggs from the parasitic female hatch in the small intestine, and the larva, 450 to 600 microns (1/55 to 1/40 inch) long and 16 to 20 microns (1/1560 to 1/1250 inch) in diameter, is found in the feces. The eggs are at times passed from the female in a chain, and when there is diarrhea they may appear in the feces singly or in a chain. In water or moist earth at 20° C (68° F.) or above, the larvæ develop in two or three days into the adult male and female worms, and copulate; the females pass eggs which hatch a rhabditiform larva; this larva molts to form a strongyloid larva which passes through the skin just as does the strongyloid larva of the hookworm. The larva, passing through the skin, travels just as does the hookworm larva to the lungs, up the trachea and down the esophagus and through the stomach to the duodenum, where it develops into the adult parthenogenetic female which burrows into the mucosa of the intestinal wall and passes the eggs which hatch in the intestine.

The strongyloid larva may be taken into the stomach with food and drink. Fülleborn and Torgau found that, under such conditions, the larvæ pass through the stomach wall to the blood stream, and to the lungs and down the esophagus, just as they do when they penetrate the skin.

At times, especially in cooler regions, when the temperature is not above 15° to 18° C. (59° to 64.4° F.), the free-living generation may be missing, and the worm tends to be strictly parasitic: The larvæ passed in the feces molt and form directly the strongyloid larvæ, which penetrate the skin or are taken in with food and drink, and develop to the parthenogenetic females in the small intestine. Strong transmitted the infection to monkeys by feeding infected feces to them.

(*c*) *Habitat.*—The parasitic female burrows into the wall of the small intestine, just as does the female trichinella. But strongyloides does not burrow so deep, and the vulva is farther back in the body than is the vulva of trichinella. As a result, the larvæ of strongyloides are passed among the folds of the intestinal mucosa, and pass out into the intestinal contents. At times the embryos of strongyloides may get into the circulation.

Epidemiology.—The strongyloid larva enters the body through the skin, or at times with food and drink through the mouth, in the same way as the hookworm larva enters. Since the distribution of strongyloides is the same as that of the hookworm, and the two worms enter the body in the same way, the infection is spread the same way in both cases.

Diagnosis.—The diagnosis is made by finding the larvæ in the feces.

Treatment.—The worms are not readily expelled; but **oil of Chenopodium or thymol,** given as for hookworms, will expel part of them. Stiles considers that **flowers of sulphur** may be of value in the treatment of the infection.

Pathogenic Action.—It is not uncommon to find the larvæ of this worm in the feces, without there being any intestinal disturbance. It is probable that a large number of worms in the small intestine would cause some irritation and catarrhal inflammation; but the worm does not cause diarrhea, as was formerly thought. In Saigon, Brau found persons with eosinophilia of 25 to 69 per cent., and only strongyloides larvæ to account for it.

The worm is very commonly found in monkeys, where it causes no disturbance.

History.—The worms were found by Normand, in 1876, in the stools of persons with diarrhea and dysentery from Cochin China, and were considered to be the cause of Cochin China diarrhea. Further study has shown that the worm is fairly common throughout the world, but that it is not connected in a causal way with Cochin China or other diarrheas.

Geographical Distribution.—The distribution of the worm is very much the same as the distribution of the hookworm. It is common in tropical and subtropical regions, and in mines. It is not uncommon in the southern part of the United States. Lucke found it sixteen times in his examination of healthy soldiers in Kentucky.

B. NEMATODES OF THE BLOOD AND LYMPH

(e) FAMILY FILARIIDÆ

With the constantly increasing number of nematode embryos found in the blood of vertebrates, it has been necessary to split the old genus Filaria up into several other genera.

The family Filariidæ is now divided into a number of genera, of which six are of interest to us: Filaria, Loa, Onchocerca, Acanthocheilonema, Dirofilaria, Agamofilaria, and Dracunculus.

The filariidæ are long, slender, thread-like worms, the adults living in the lymphatics, the serous cavities, the heart, and the subcutaneous tissues. The embryos circulate in the blood, or rarely are evacuated to the exterior. Where known, the development always requires an intermediate host.

7. *Filariasis*

Synonyms.—Synonyms for the adult worm are: *Filaria wuchereri, Filaria taniguchi;* for the larvæ are: *Filaria sanguinis-hominis, Filaria nocturna.*

Definition.—Filariasis is the name given to the condition resulting from infection with worms belonging to the genus Filaria. It is generally understood to mean infection with *Filaria bancrofti,* Cobbold, 1877.

The genus Filaria, as now understood, includes what is left of the old genus Filaria; and there are no characteristics of the genus. A number of filariæ are parasitic in the lymphatic system of man; but only one has been shown to have any pathogenic action.

Etiology.—PREDISPOSING CAUSES.—*Race.*—There is no racial resistance to the infection. Daniels' tabulation of cases in British Guiana shows infection to be more common in native whites than in negroes, while Indians (living under different conditions, however) were free from infection.

Sex.—There is no difference in sex susceptibility, though generally the percentage of infection is higher in males than in females, probably on account of greater exposure of males to infection. Daniels' tabulation shows a higher percentage of females infected in white and mixed races; while there is a higher percentage of males infected in the negro race.

Age.—There is no age susceptibility, though the infection is rare in children under ten years of age. It is most common in young adults, from thirty to forty years of age; and it is less common in old persons, though constantly exposed to infection. Todd and Wright, in studying an endemic center of filariasis near Cairo, tabulated the age incidence of the infection: up to nineteen years, 23.15 per cent.; twenty to forty years, 31.7 per cent.; forty to sixty years, 28 per cent.; over sixty years, 1 in 8 persons.

Climate.—The infection is more common in towns than in the country; and it is more common along the seacoast and along large rivers. Warmth and moisture are important, as warmth favors development of the larva in the mosquito, while the warmth and moisture make the larvæ more active and favor them in getting from the proboscis of the mosquito through the skin of man.

Season.—There is no seasonal prevalence, on account of the long time it takes for the development of the adult worm. Martinez says that in Porto Rico there are seasonal fluctuations in the acute conditions accompanying filariasis, these conditions being more common in April and May and from July to October.

EXCITING CAUSE.—The condition is due to *Filaria bancrofti.* The adult worms live in the lymphatic system, and the larvæ circulate in the blood. The worm goes through a cycle of development in the mosquito, which acts as the intermediate host.

(*a*) *Morphology.*—The adult worms have the appearance of white hairs. The anterior end is bluntly rounded; the mouth is round, 8 microns (1/3000 inch) in diameter, and without lips. The male worm is from 4 to 4.5 centimeters (1 3/5 to 1 4/5 inches) long, and 0.1 millimeter (1/250 inch) in diameter; the posterior end is broadly rounded and is coiled like the tendril of a vine; the genital opening is at the posterior end; there are two unequal spicules, and it is generally stated that there are three pairs of pre-anal and three pairs of post-anal papillæ. The female is 8 to 10 centimeters (3 1/5 to 4 inches) long, and 0.24 to 0.3 millimeter (1/100 to 1/80 inch) in diameter; the posterior end is rounded; the body is nearly filled by the two uterine tubes which join at the vulva, 1 to 1.3 millimeter (1/25 to 1/20 inch) from the anterior end; the uterine tubes are filled with eggs, 40 microns (1/600 inch) by 25 microns (1/1000 inch), which change to straightened-out embryos near the vulva. The worm is viviparous.

(*b*) *Habitat of the Adult.*—The adult worms live in the lymphatic vessels of man, males and females together—the females being about twice as numerous as the males—coiled up in a mass which at times obstructs the lymph circulation and produces local inflammation.

Frequently dozens of worms are present. Thirteen worms have been found in an enlarged epitrochlear gland. The worms live from 6 to 13 years; they are very resistant; live several days after death of the host; survive attacks of fever that kill the larvæ; and may be found alive in the pus of an abscess. Prolonged suppuration kills them, and a dead worm, or pieces of a worm, may be found in the pus of an abscess. When the worms die or are killed, they may calcify; and it is probable that they may be absorbed later.

(*c*) *Habitat, Morphology, and Biology of the Larva.*—As the egg passes from the ovary to the vulva, the embryo develops, and then straightens out, retaining the egg membrane as a sheath. At times the eggs are passed before the embryo straightens out, and the eggs thus passed have been considered as playing a part in the cause of elephantiasis, by plugging the lymphatic vessels. These eggs must come from dead worms, as the egg cannot pass the vulva until the embryo has straightened out. The term *microfilaria* is used to designate the filarial larvæ.

As passed from the female, the larva is 240 to 320 microns (1/100 to 1/180 inch) long, and 7.5 to 8.5 microns (1/3300 to 1/3000 inch) in diameter, and has a sheath which is longer than itself. As the larva moves back and forth in the sheath, the sheath falls together at the anterior and posterior ends, like an empty finger in a glove. The sheath is elastic, like a rubber band, and it may be drawn out to a long band when it becomes attached to the slide and the larva tries to escape. The larvæ wriggle actively, but travel slowly, like a snake or an eel on a slippery surface.

The anterior end of the larva is variously described as having a mouth, a number of lips and a retractile spine. Fülleborn is of the opinion that there is a mouth, but that the lips result from irregular retractions of the body wall, and that the appearance of a spine is an optical delusion. The body is covered with a striated cuticle, and contains a central column of large cells with embryonic nuclei. The chain of nuclei is broken in several places, leaving clear spots which represent rudimentary organs. These spots have been given names; and, as they vary in position in different species of filariæ, they are of importance in classification and diagnosis.

The larvæ remain alive for months or more in the circulating blood. While it is not known how long the larvæ live in the blood of man, the larvæ of the dog filaria, when injected into uninfected dogs, remain alive for two or three years. It is generally considered that the larvæ grow somewhat in the blood; but here again, it is not possible to say definitely regarding filarial larvæ in man. Fülleborn injected the larvæ of *Filaria repens* into uninfected dogs, and in two years and nine months the larvæ had grown to double their size when injected. Dead larvæ may be seen circulating in the blood, and their remains, at times calcified, may be found in the liver and kidneys.

The microfilariæ may be present in the blood in large numbers—300 to 600 in a drop of blood. On this basis, there would be from 30 to 50 million microfilariæ in the body, if they were evenly distributed. But they are unevenly distributed in the body, being numerous in the capillaries—especially the lung capillaries. Yorke and Blacklock found them more numerous in cutaneous blood than in blood from the median basilic vein. They pass into the secretions and excretions—urine, saliva, and conjunctival secretion—aside from their presence as a result of the rupture of lymph-vessels. They do not pass the placenta.

The microfilariæ do not stand drying well. They stand changes in osmotic pressure, as they are adapted for such change when taken into the digestive tract of the arthropod host. Slight warming increases their activity; greater warming kills them. They stand cold well, living a week at room temperature, and six to seven weeks in the ice-box; freezing kills them. They are not affected by light, the roentgen rays or electric current. Ordinary chemical antiseptics kill them.

(*d*) *Periodicity.*—The microfilariæ are abundant in the peripheral blood at night, but disappear or become much less numerous during the day. For this reason the name *nocturna* has been given to them. Change in sleeping habits brings about a gradual change in the periodicity; and Yorke and Blacklock found that the periodicity was completely changed in eleven days. When sleep is in short periods, the periodicity is entirely lost; and there may be no periodicity in persons whose habits of sleep are regular, as in the South Sea Islands.

Manson showed that the microfilariæ are collected in the capillaries of the lungs, the heart-muscle, and in the large arteries of the thorax and neck, during the time they are absent from the peripheral circulation.

The usual explanation of the periodicity is that it is connected in some way with sleep; but no satisfactory explanation of the periodicity has been given. The nocturnal periodicity is of advantage to the filariæ, as *Filaria bancrofti* is transmitted by night-biting mosquitoes. In

Fiji, where *Filaria bancrofti* shows no periodicity, the infection is transmitted by a day-biting mosquito.

(*e*) *Evolution.*—The larvæ of *Filaria bancrofti* develop in certain mosquitoes which act as the intermediate host for the infection.

The larvæ, taken into the mosquito's stomach with the blood, do not multiply, but they appear to become more numerous as a result of the coagulation and condensation of the blood in the mosquito's stomach. The coagulation of the blood entangles the sheath, and in 1 or 2 hours the larva escapes from the sheath; it passes through the stomach wall in 6 to 12 hours, and in 18 to 24 hours reaches the thoracic muscles where it undergoes development.

In the beginning of its development in the thoracic muscles of the mosquito, the larva lies quietly, stretched out between the muscle bands; and it increases in thickness and shortens, so it comes to be sausage-shaped. Later the larva increases in length, so that the fully developed larva is 3 to 4 times as thick and 3 to 5 times as long as when taken into the stomach of the mosquito. The fully developed larva becomes active, bends or curls up and, leaving the thoracic muscles, it enters the general peritoneal cavity, from where it can pass to any part of the body. A special chemotactic action causes the fully developed larvæ to accumulate in the labium and about the pharynx; but some of them pass to different parts of the body, even to the legs and palps. The fully developed larva is 1 to 1.8 mm. (1/25 to 1/14 inch) long and 24 to 32 microns (1/1000 to 1/780 inch) in diameter, has a complete digestive tract, and resembles the adult worm in structure.

The length of time necessary for development in the mosquito varies with the atmospheric temperature. Lebredo, in Havana, found that development was complete in 15 days, at 25.5° C. (77.9° F.); and in 19 to 23 days, at 21.8° C. (71.2° F.). Ten days is the shortest time in which complete development has been observed; and the time required for development is usually given as 14 or 15 days.

There may be thirty or more fully developed larvæ in a mosquito, and they may be so crowded into the labium that the other parts of the proboscis are forced out of the groove in the labium. When the mosquito bites man, the larvæ escape from the labium through Dutton's membrane, onto the skin, and quickly pass down the hair follicles and through the skin; or they may, at times, pass in through the wound made by the bite, after the biting parts have been withdrawn. All or nearly all of the larvæ escape from the labium during a single act of biting.

The development of the filariæ after they enter the body of man is not known. Apparently the worms grow rapidly at first, as clinical symptoms may appear in 1 or 2 months after infection; but it is probable that it takes 8 months or longer for them to reach sexual maturity and to begin to pass larvæ into the circulation.

Epidemiology.—The infection is spread from man to man by mosquitoes; and, as far as is known, no other animal than man harbors *Filaria bancrofti*.

Different mosquitoes act as the intermediate host in different parts of the world. *Culex quinquefasciatus* is the intermediate host in the West Indies and in Charleston, the latter being the only endemic center in the United States. *Myzomyia rossii* is the intermediate host in India; *Stegomyia pseudoscutellaris* in Fiji; *Pyretophorus costalis* in Nigeria; and *Panoplites africanus* in Central Africa. Other mosquitoes that act as intermediate hosts are *Myzorhynchus minutus, Myzorhynchus nigerrimus, Mansonia uniformis, Mansonia pseudotitillans,* and *Cellia albimanus.*

While the larvæ can complete their development in some mosquitoes, and those mosquitoes can act as intermediate hosts, the larvæ do not get beyond the "sausage" stage of development in the thoracic muscles of other mosquitoes; and in still other mosquitoes the larvæ die in the stomach. The same mosquito may act differently toward the same species of filaria in different regions.

The distribution of the infection is unequal in any region, being more common along the sea coast and along large rivers. But there are circumscribed endemic areas, beyond which the infection does not spread, though the same mosquitoes exist in the surrounding territory as in the endemic area. Charleston, South Carolina, is an endemic area; but the infection does not spread to the surrounding towns. Francis found 3 cases in Columbia, South Carolina; 3 cases in Tampa, Florida; 2 cases in Jacksonville, Florida; and 1 case in Beaufort, South Carolina—all from Charleston or Cuba. But, though the proper mosquitoes are present, the infection does not spread from these cases in these cities. Daniels reports that filariasis is very rare at the southern end of Lake Nyassa, while it is very common at the northern end. Todd and Wright report an endemic area of filariasis near Cairo, but the infection does not spread to the surrounding country, though the proper mosquitoes are abundant.

Francis shows that, in order to bring about the transmission of filarial infection, the infecting individual must harbor a large number of microfilariæ in his blood; he must be bitten by a large number of mosquitoes in order that some of the mosquitoes may become infected; and a large number of mosquitoes must bite the individual who is to become infected. That is, in order for the infection to spread, there must be mass infection, and there must be mass mosquito biting; and he considers that Charleston became an endemic area as a result of the landing in the city of a shipload of slaves from an area of heavy infection in Africa, and that the slaves were crowded together where they were exposed to mosquito bites. He explains the non-spread of the infection in cities to which infected Charlestonians have been transported, by the absence of mass blood infection in the transported cases and the absence of mass mosquito biting of those cases in their new locality.

Under natural conditions, a rather high percentage of the transmitting mosquitoes are infected. In the rooms occupied by filarial patients in "The Old Folks' Home" in Charleston, Francis found 20 per cent.

of *Culex quinquefasciatus* infected with filarial larvæ. In a hospital in Barbados, where 12 to 13 per cent. of the persons had microfilariæ in their blood, Low found 23 per cent. of *Culex quinquefasciatus* infected with filarial larvæ in various stages of development, and one mosquito had fully developed larvæ in the labium. In experimental work, it is found that a very large percentage of infected mosquitoes die, so that, of 100 infected mosquitoes, none or only a few will live to have fully developed larvæ; and in order to obtain fully developed larvæ it is necessary to feed the mosquitoes on blood that does not contain too many larvæ—Bahr advises about 40 to 60 larvæ to 16 cubic millimeters of blood. If the mortality among naturally infected mosquitoes approaches that among experimentally infected mosquitoes, it would appear that this mortality would be of importance in keeping down the number of heavily infected mosquitoes.

Clinical Manifestations.—The large majority of persons who are infected with *Filaria bancrofti* have no symptoms at all; and the infection is discovered only in a routine examination of the residents of a locality. The presence or absence of symptoms varies greatly in different localities. Thus, in the Philippine Islands, where 15 to 20 per cent. of the inhabitants may have the infection, it is very rare to see any symptoms resulting from it. On the other hand, in the region of Amoy, China, elephantiasis is very common among the persons who are infected with filariæ. In Charleston, Jackson found symptoms in only 5 per cent. of the infected persons. In Fiji, Bahr says that one-half of the men and one-fifth of the women have symptoms due to filariæ; and in French Guiana, Clarac says that there are few inhabitants who, after they reach a certain age, do not have some symptoms due to filariæ. In the Comoro Islands, Ruffiandis says that 80 to 90 per cent. of the inhabitants have some symptoms due to filariæ; and in the island of Mayotte, about half of the men are impotent as a result of the damage from scrotal elephantiasis.

The more common manifestations are (1) filarial lymphangitis, (2) lymphatic tumors, (3) lymphorrhagia, and (4) elephantiasis.

(1) FILARIAL LYMPHANGITIS.—(*Endemic Lymphangitis, Elephantoid Fever, Pernicious Lymphangitis, Erysipelas of Rio, White Erysipelas*).—The condition has the local and general symptoms of acute infection of the lymphatics. It may begin with a chill. The temperature rises to from 38.3° to 40° C. (101° to 104° F.); and there is redness and pain along the course of some of the superficial lymphatics, more commonly on the leg. The adjacent lymph-glands may be enlarged and tender.

The condition is generally due to streptococcus. Rose obtained a pure culture of streptococcus from 15 of 17 cases of filarial lymphangitis.

The fever subsides in two or three days, and there is ordinarily no lesion remaining. At times the lymph-vessel may remain as a hard cord, and on section an adult worm may be found. Abscesses (*filarial abscesses*) may develop along the course of the affected lymphatics or in various parts of the body, especially in the deep tissues—as the kidney, retroperitoneal tissues, epididymis, or in the thorax. Muscle abscesses are fairly common; and Wise and Minett found parts of worms or complete worms in the contents of 22 of 28 muscle abscesses.

Septicemia may develop, and may be fatal.

The altered lymphatics increase the severity of the condition, and it tends to recur.

The *diagnosis* of the condition is made from the local signs. When the condition is severe it may be confused with plague; and Martinez reports a fatal case of filarial lymphangitis with two slightly enlarged and very painful glands in the right groin, and blood, casts and albumin in the urine. Filarial embryos were found in the blood; and there was no evidence of plague at the postmortem examination. Castellani and Chalmers note that the condition may be confused with caterpillar sting.

Prophylaxis consists of **good hygiene, the wearing of shoes and avoiding injuries of the skin, keeping the skin clean, eating good food, and building up the general resistance of the body.** When possible, the patient should remove to a **cool climate.**

Treatment is the same as for any acute lymphangitis; **rest in bed, and local applications to the affected parts.** Rose reports good results from the use of a **vaccine prepared from several strains of streptococcus isolated from the cases. Abscesses should be opened,** and treated as abscesses from any cause.

(2) LYMPHATIC TUMORS.—(*a*) *Adenolymphocele* (*Varicose Groin Glands, Helminthoma Elastica, Varicose Lymphatic Glands*).—The condition is most common in the groin and inguinal glands; the axillary glands are next frequently affected; and any glands—even the lumbar glands—may be involved. The glands are enlarged and elastic. They diminish in size at night; and are more enlarged after each attack of lymphangitis. Quite frequently the enlarged glands, instead of being elastic, are hard.

The condition may be mistaken for hernia, lipoma, or tuberculosis. When punctured, lymph or chyle is obtained, and it may contain microfilariæ.

Ordinarily the **tumor** is not large enough to cause any inconvenience; but it may become very large. When it is so large as to discommode the patient, it **may be removed**; but it will return, as it is part of a more extensive condition. **Great care is necessary to avoid infection** if the tumor is removed.

(*b*) *Filarial Tumors of the Testicle and Spermatic Cord.*—(i) Filarial Orchitis.—There are symptoms of acute orchitis: the testicle swells and is painful, and there is effusion into the tunica vaginalis. The symptoms subside quickly, but there is a tendency for the fluid to remain as a hydrocele.

The *treatment* consists in **rest in bed** and **local applications to the affected parts.**

(ii) Lymphatic Varicocele.—The lymphatics of the spermatic cord are dilated and tortuous. The condition is often accompanied by hydrocele.

Treatment consists in wearing a **suspensory bandage**; or, if the mass is large enough to discommode, it **may be removed.**

(iii) Pedicled Inguinoscrotal Lymphangioma.—This condition is an elastic tumor that resembles an epiploic hernia, attached to the spermatic cord. It can be reduced.

Ordinarily it causes no particular disturbance; but it **may be removed** if it discommodes.

(3) LYMPHORRHAGIA.—(*a*) *Internal Lymphorrhagia.* (i) Chyluria, Hematochyluria and Lymphuria.—When the thoracic duct is obstructed and the lymphatics about the kidneys, ureter and bladder are dilated, rupture of the dilated vessels allows chyle to escape into the urinary tract and to appear in the urine (*chyluria*). When blood appears with the chyle, the condition is known as *hematochyluria*. When the obstruction is below the thoracic duct and receptaculum chyli, there is *lymphuria.*

The condition is usually more common in women than in men.

An attack of chyluria may be brought on by emotion or by exercise. It may come on after operation for removal of glands or lymph vessels in the inguinoscrotal region. Hematochyluria may result from coëxistent infection with bilharzia and filaria.

The onset of an attack is usually sudden, without symptoms; and the first the patient notices is that his urine is milky or bloody. There may be pain in the back, and slight fever. The urine may be bloody at first, and milky later; or it may be milky from the start. The urine coagulates on standing, and a thin white layer collects on the surface. There may be clots in the urine as passed; and they may cause strangury. The morning urine may be clear, and the later urine milky, or bloody, or "coffee and milk" in color.

The course is irregular. There may be short attacks, with long intervals; or the condition may continue for years.

Prolonged passage of blood causes anemia; but chyluria in itself does not produce any great disturbance.

The *diagnosis* is made by examining the urine, and by the presence of other lymphatic disturbances. The condition must be differentiated from hemoglobinuria; and search must be made for the eggs of bilharzia.

The *treatment* consists of **rest in bed,** and **symptomatic treatment.** There are reports of cures from salvarsan, neosalvarsan, atoxyl, thymol, methylene blue, and other drugs; but generally no drugs internally or injected into the bladder are of any curative value. **Urinary antiseptics, as urotropin or salol,** may be given to lessen the danger of infection of the bladder. **If the urine clots in the bladder, it should be washed out**; or it may be necessary to **open and drain the bladder.**

(ii) Chylous Hydrocele (*Chylocele*).—This is caused by the same condition of the lymphatics as that which causes chyluria. It may develop without symptoms, or may follow an attack of orchitis. There are other evidences of lymphatic obstruction. The tumor is not translucent; and milky fluid is obtained on puncture.

Under the conditions which cause lymphuria, there may be a *lymphocele*.

As the mass does not become large, no treatment is necessary; or **occasional tapping** is all that is required. It may be removed by **operation**; but it will recur.

(iii) Chylous Ascites.—A few cases of chylous ascites have been met with.

(iv) Chylous Diarrhea is rare.

(*b*) *External Lymphorrhagia.*—External lymphorrhagias may occur on any part of the body in which there are dilated lymphatics, but they usually occur on the scrotum of man and on the labia majora of woman.

(i) Lymph Scrotum.—The condition may begin with fever, pain, and redness and swelling of the scrotum; or the enlargement of the scrotum may be without symptoms of inflammation. The entire scrotum is swollen and elastic; and there are a number of small clear vesicles on the scrotal skin. These vesicles may rupture spontaneously, and a clear, coagulable fluid escapes. Under the conditions which cause chyluria, the fluid may be milky. Microfilariæ may be found in the fluid; and filarial eggs have been found in it.

Bacterial infection is common; and the condition is frequently associated with elephantiasis of the scrotum.

The *treatment* is **symptomatic**, as the condition is part of a more extensive condition. The **parts should be kept clean,** in order to lessen the danger of infection. **All affected tissue may be removed, and dilated lymphatics ligated**; but the condition will recur, and the operation may be followed by chyluria.

(ii) Lymphangiectasis of the Labia Majora.—This is the same condition as lymph scrotum. The superficial lymphatics are dilated, and there may be vesicles which exude lymph. Infection is common.

The dangers and treatment are the same as in lymph scrotum.

(iii) Other Lymphangiectases.—Lymphangiectases may occur on the legs or on the arm, or any part of the body.

(4) ELEPHANTIASIS (*Elephantiasis Arabum*).—Elephantiasis is characterized anatomically by a chronic inflammatory process that involves especially the connective tissue and the walls of the lymph and bloodvessels, and by edema and serous transudates. It is characterized clinically by a progressive local hypertrophy.

While elephantiasis may be due to various causes, the form under discussion is due to *Filaria bancrofti* plus repeated attacks of lymphangitis or erysipelatous inflammation, usually due to streptococcus.

There are two phases in the evolution of elephantiasis. In the beginning, there is acute, diffuse inflammation of the vascular and connective tissue of a portion of the body, with a marked tendency to edema and hyperplasia of the connective tissue of the skin and subcutaneous tissues. The developed disease is characterized by fibrous hypertrophy of the tissues of the affected part.

The condition is progressive, the first phase being marked by repeated attacks of lymphangitis and erysipelatous inflammation. As the condition progresses, the skin becomes thick, hard and deformed; and it cannot be pitted with the finger. The epidermis may be smooth or scaly, moist or dry.

In 95 per cent. of the cases the lower part of the body is involved. In most regions the leg is most commonly involved; but in some regions the genital organs are most commonly affected.

(*a*) *Elephantiasis of the Lower Limbs.*—The leg is usually involved; rarely the thigh alone.

With repeated attacks of lymphangitis, the leg becomes enlarged, and the skin becomes thick, and is thrown into transverse folds. The foot may not be involved until late, and the thick skin of the leg hangs over the apparently healthy foot. Usually the foot is swollen, and the thick skin of the leg hangs over it in a thick fold.

Débris and skin secretions collect between the folds of the skin, where they decompose, thus increasing the danger of infection and leading to the formation of ulcers. Later the skin becomes dry and scaly, the nails are thick, and the hairs fall out. The epidermis may be thickened and thrown into an irregular, dark, warty surface—the verrucous form of elephantiasis.

Prophylaxis is an important consideration. As treatment of elephantiasis is difficult, and frequently is only palliative, it is important to **prevent the development of the condition.**

Lymphangitis should be prevented in persons with filariasis. **Shoes should be worn, and the skin should be kept clean. All wounds should be kept clean. Mosquito bites should be prevented,** not only to prevent the spread of filariasis, but also to prevent bacterial infection from the scratching of bites. Persons with filarial infection should **leave the tropics, or should live in a higher region.**

Lymphangitis should be carefully treated, and the **general health should be toned up.**

Treatment should consist of the following measures: The **skin should be kept clean, and not irritated or broken.** The most satisfactory method is that developed by Castellani. The patient is kept in bed, with the limb elevated, and 2 to 4 c.c. (1/2 to 1 dram) of **Merck's fibrolysin** is injected into the affected parts or into the gluteal muscles daily for from three to six months, with occasional interruptions of a few days. The limb is constantly kept tightly bandaged with **flannel bandages. Rubber bandages** macerate the epidermis; but Castellani prefers them for cases of the verrucous variety of elephantiasis, where the skin is rough and warty. The pressure should be evenly distributed, and, in order to make pressure on the hard areas of skin, **small bags of shot** may be placed over these areas under the bandage.

A solution of **resorcin and salicylic acid,** 2 grams (31 grains) of each in 120 c.c. (4 ounces) of alcohol, may be applied to the skin to remove the horny masses in the verrucous variety.

Massage may do good.

After the limb has been reduced in size, and the skin has become soft, long strips of the **redundant skin may be removed, and the wound closed.**

Operative treatment consists of removal of affected tissue and plastic operation if the limb is still useful, or amputation if the limb cannot be made useful; but such treatment is not satisfactory.

(*b*) *Elephantiasis of the Scrotum.*—The condition is rare before puberty. With repeated attacks of lymph scrotum or erysipelatous fever, the scrotum becomes enlarged, and the scrotal skin becomes thick and hard. The scrotal skin does not undergo the marked changes that take place in the skin of the leg. The skin is thick below, and there may be deep creases in it; above, the skin is thin, and passes into the normal skin over the pubes. The superficial lymphatics are frequently dilated to form varices. The lower part of the tumor may ulcerate.

The testicles are at the upper and back part of the tumor, or they may be drawn down by the gubernaculum, or they may be involved in the process. There is usually hydrocele, at times chylous.

The penis is rarely involved in the process; but it is buried in the mass, and in the upper part of the mass is an opening which leads down to the penis.

The mass may attain an enormous size, weighing 100 pounds or more —the largest reported weighing 224 pounds.

Prophylaxis consists in the prevention of lymphangitis, in the same way as in the prevention of elephantiasis of the leg. **Vermin should be prevented about the scrotum and pubes**; and, in removing vermin, **care should be taken not to break the skin.**

Treatment is **operative removal of the affected tissue.** With a tourniquet about the neck of the tumor, the skin flaps to cover the penis and testicles are marked out in the healthy skin, and the mass is removed, first separating the cord and testicle from the mass, and opening the hydrocele, and then separating the penis, with a sound in the urethra, care being exercised not to injure the dorsal arteries and veins. After removal of the mass, the penis and testicles are covered with the flaps of healthy skin. **Strict asepsis and hemostasis** are very important.

(*c*) *Elephantiasis of the Upper Limbs.*—This condition is rare by itself: usually other parts of the body are also affected. It usually involves the forearm or hand, or sometimes the arm. The process is the same as in the leg. The epitrochlear glands are swollen, and there is pain in the region of the glands. Lymphangitis and erysipelatous attacks are less common than in the legs.

If the condition discommodes the patient, the **affected tissue may be removed.**

(*d*) *Elephantiasis of the Penis.*—The condition may affect part or all of the penis. It becomes large, ending in the hypertrophied prepuce. The penis may be involved with, and to a greater extent than, the scrotum.

Treatment consists in **removal of the elephantoid tissue.**

(*e*) *Elephantiasis of the Labia Majora and Clitoris.*—This is a common condition, and the mass may weigh from 10 to 30 pounds. It is the same condition as elephantiasis of the scrotum and penis. The labia minora and the prepuce of the clitoris may be involved, the prepuce of the clitoris forming a mass as large as a child's head. Lymphorrhagia is common.

Treatment consists in **removal of the mass.**

(*f*) *Elephantiasis of the Mammæ.*—This condition may involve one or both breasts. The mass may weigh as much as 20 pounds, and may reach to the pubes. The edema is softer than in elephantiasis of other parts of the body. The condition may be accompanied by acute, subacute or chronic mastitis, and is usually associated with lymphadenocele in the axilla.

Treatment consists of the **usual operation for removal of the breast.**

(*g*) *Elephantiasis of the Face and Head.*—This condition is rare. It may involve only the nose, eyelids, lobes of the ears or scalp.

Treatment consists of **removal of the affected tissue and plastic operation.**

Prognosis.—No treatment has any curative action.

When there are symptoms there is generally no danger to life, except that due to the secondary infections. Lymphangitis, abscess, and septicemia may prove fatal. The various lesions are the cause of varying degrees of incapacity of the patient, depending upon the mechanical interference of the lesion. In some regions the scrotal involvement causes inability to procreate in about one-half of the males, and, consequently, it is a cause of lowering of the population.

Pathogenic Action.—The blood of persons infected with *Filaria bancrofti* shows an eosinophilia, and there is a local eosinophilia about the adult worms, the eosinophilia probably being caused by some product of the worm. There does not appear to be any variation in the eosinophilia, corresponding to the periodicity of the microfilariæ. Generally there is no anemia in persons infected with *Filaria bancrofti,* unless there is secondary bacterial infection; but some observers have reported anemia in persons with nothing but *Filaria bancrofti* infection to account for it.

In some regions, persons infected with *Filaria bancrofti* have short attacks of fever, which do not seem to be due to secondary bacterial infection. There is frequently pain in the chest, dyspnea, and cough; but there are no changes in the lungs. There may be plugging of the retinal blood-vessels by dead larvæ; and there may be hemorrhages into the retina.

The adult worms, living in the lymphatics, may cause obstruction, or they may cause irritation and inflammatory thickening of the vessel wall, with narrowing of the vessel. Bahr is of the opinion that the worm has an action on the tissues, which causes proliferation of the endothelium lining the vessel and a fibrous thickening of the vessel wall. The position of the obstruction determines what the symptoms shall be. There is lymph stasis, and, if the thoracic duct is involved, the lymph will be milky.

When the thoracic duct is obstructed there is stasis below the obstruction, and through the anastomosing vessels this leads to widening of the lymph vessels in the abdomen and pelvis, including those surrounding the kidneys and bladder. This stasis may cause *lymph scrotum* or *varicose groin glands;* while rupture of the lymph-vessels pours the milky lymph into the serous cavities and causes *chylous effusion* into the tunica vaginalis or abdominal or pleural cavities, or into the urinary tract, causing *chyluria.*

The adult worms frequently get into the spermatic cord, where the obstruction to the flow of lymph causes *orchitis* or *funiculitis;* and, if there is bacterial infection, there may be *septic funiculitis. Filarial abscesses* are associated with bacterial infection.

The obstruction may cause dilatation of the superficial or deep lymphatic vessels in various parts of the body; and the lymph-glands involved in the lymph stasis are dilated and soft (*adenolymphocele*); or when the vessels leading from the gland, or the gland itself, are occupied by the worm, the gland is converted into a hard mass. Dilated lymph-tissues may cause transitory swellings in different parts of the body.

Lymph stasis ordinarily causes only edema; but it may cause enlargement of the lymph-spaces and an increase of fibrous tissue in the subcutaneous tissue. But the changes in the lymph-vessels predispose to secondary bacterial infection; and repeated attacks of lymphangitis and erysipelatous fever (*elephantoid fever*) lead to the chronic changes in the skin. There is hypertrophy and sclerosis of the dermis, with enlarged lymph-spaces; and later there is hypertrophy of the epidermis; that is, the entire condition is that of elephantiasis.

While the recurring attacks of lymphangitis are the principal cause of elephantiasis, Manson has suggested that the eggs of the filariæ may block the lymphatics, and play a part in the production of the condition; but this must be very rare, and it is probable that the eggs would lead only to lymph stasis.

It is not possible to explain why elephantiasis is common in some filarial regions and not in others, though it has been suggested that the bacteria causing the secondary infection are more virulent in some localities than in others. Neither is it possible to explain why elephantiasis affects one part of the body in one locality and another part of the body in another locality; why children seldom have elephantiasis; why it occurs more commonly in men than in women; and why it occurs mainly between the ages of 30 and 40 years; or why chyluria is common in one region and not in another, and why it is more common in women than in men.

It is to be borne in mind that a very small percentage of cases of filariasis ever develop elephantiasis; and that, on the other hand, elephantiasis is not necessarily caused by filariæ; but any obliterating lymphangitis may cause it. Thus, elephantiasis may be caused by acute or chronic lymphangitis, leprosy, syphilis, tuberculosis, injuries, varicose ulcers, or phlebitis.

Quite frequently there are symptoms when it is impossible to find microfilariæ in the blood; and it is usual to fail to find microfilariæ in the blood in cases of elephantiasis—Cruikshank and Wright found them in 12 of 130 cases. The worms may not have reached sexual maturity, or there may be only male or only female worms present. The adult worms may not be numerous, so the microfilariæ are scarce in the blood, and are not found on examination. Rodenwaldt and Fülleborn showed experimentally that, when five adult *Filaria repens* females were transplanted into a medium-sized dog, it was two and one-half months before the microfilariæ could be found in the centrifuged blood; and three weeks later, there were ten microfilariæ in fifteen drops of blood. From this, it is evident that the adult worms must be present in fair number, before the microfilariæ can be found in the blood; and it takes some time for the microfilariæ to accumulate in the blood. The microfilariæ may be killed by some inflammatory condition in the host. In elephantiasis, the condition is due to secondary bacterial infection, and the infection may kill the larvæ or the adult worm. Since in elephantiasis the lymph-vessels in which the worm lies are blocked, it is to be expected that the microfilariæ would at times fail to get into the circulation; and at times the microfilariæ may be found in the tissues in elephantiasis, but not in the circulation.

There is no race, age or sex immunity or resistance to infection with *Filaria bancrofti*. Occasionally one person in an infected family escapes infection; but it is not known whether this is individual immunity. It is possible that there is acquired immunity, as the infection tends to die out in old people; and there is not repeated re-infection, though the person is constantly exposed.

Pathology.—The adult worms are found in the lymphatic vessels in various parts of the body, and the alterations in the lymphatic system are a striking feature of the disease. As the obstruction is frequently in the lymphatics draining the abdomen, the lymph-vessels of the abdomen and pelvis are dilated and the glands are lost. The lymph-vessels in the mesentery may be dilated, and there may be chylous ascites.

There may be dilatation of the lymphatics in the skin (*superficial lymphatic varix*); or the trunk lymphatics may be as large as goose quills, and their walls may be thickened (*varix of the trunk lymphatics*). When there is lymphangitis, the walls of the lymphatics are inflamed and thickened, and there may be abscesses in the lymphatics or in various parts of the body containing living or dead worms. There may be dilatation of the lymphatics of the spermatic cord (*lymphatic varicocele*); or there may be a fat-like mass attached to the cord, this mass being composed of a new growth of lymph-vessels which are dilated and have thick walls (*pedicled inguinoscrotal lymphangioma*).

Lymph-glands involved in the lymph stasis may contain numerous blood-vessels. The gland capsule is thick and fibrous; the gland tissue is converted into reticulated cavernous tissue; and the lymph-spaces are dilated and their walls are thickened. When the vessels leading from a gland are blocked, or when the worms are in the gland, the latter is converted into a hard mass of fibrous tissue.

In elephantiasis, the changes are those of lymph stasis plus those of secondary bacterial infection; and the predominant changes are edema, dilatation of the lymphatics, and cellular increase, with sclerosis. At first, only the skin and subcutaneous tissue are involved. In early cases, section allows the escape of a large amount of clear, coagulable fluid from the dilated lymphatic spaces and the connective tissue, as though the tissues had been injected with gelatin. In later cases, the fibrous tissue predominates; the skin is thickened and fibrous; and the subcutaneous tissue is replaced by trabeculæ of fibrous and fatty tissue enclosing spaces filled with yellowish, oily material; and the whole subcutaneous area exudes lymph. The bones and muscles are involved only late in the condition. The bones may be deformed and hypertrophied, and the ligaments may be ossified; the muscles are atrophied or hypertrophied and are pale and flabby. The arteries are dilated. Neuromas are common.

Microscopically, the lymph-vessels early show a round-cell infiltration, with reaction on the part of the connective tissue cells; and later there is increase in the amount of fibrous tissue in their walls. The epidermis may show little change, or it may be hypertrophied or atrophied. The cutis is fibrous and is filled with dilated lymph-spaces. The arteries show peri-arteritis and endarteritis. The muscles show cellular infiltration and fatty degeneration.

Adult filariæ and microfilariæ may be found in the tissues in elephantiasis.

History.—The condition of the leg and scrotum which we know as elephantiasis was known in India in ancient times. Celsus used the term "elephantiasis" for leprosy; and for a long time there was confusion between leprosy (*elephantiasis græcorum*) and true elephantiasis (*elephantiasis arabum*). Various writers pointed out that the two conditions were distinct; and in 1750, Hillary gave a clear description of the development of elephantiasis of the leg, and differentiated it from leprosy. Other writers confirmed Hillary, and described elephantiasis of the scrotum and other parts of the body.

In 1812 Chapotin described hematochyluria in Mauritius, and in 1832 Salese also described it. In 1835 a conference on the subject was held in Rio de Janeiro.

In 1863, Demarquay found embryo filariæ in the fluid of a chylous hydrocele in a patient from Havana; and in 1866 Wucherer found them in hematochylous urine in Brazil. In 1872, Lewis found them in the urine and blood of a patient, and gave to them the name *Filaria sanguinis hominis*. In 1875 Manson declared that filariæ were the cause of elephantiasis and of various conditions of the lymphatic system—as lymphatic varix, varicose glands, and lymph scrotum. In 1876 Bancroft found the adult worm in a lymphatic abscess of the arm. In 1878 Manson discovered that the worm was spread by mosquitoes; but he thought the worms passed from the mosquitoes into water, and that man was infected by drinking the water. Later, Bancroft suggested that the infection was transmitted by the bite of the mosquito; and Low worked out the development of the worms in the mosquito and their migration to the mouth-parts of the mosquito.

Geographical Distribution.—Filariasis is common in Turkey, Arabia, India, Indo-China, China, and Southern Japan. It is common in Oceania, and in Africa as far south as 25°. It is present in the western hemisphere from Buenos Aires on the south to the southern part of the United States on the north. In 1915 Johnson examined the blood of 400 persons in Charleston, South Carolina, and found embryo filariæ in the blood of 77 persons. Francis found embryo filariæ in the blood of a few persons in other cities in the southern part of the United States; but in every case the person gave a history of having lived in Charleston or in Cuba. The infection is common in the West Indies.

As any person who is infected with *Filaria bancrofti* may act as a source of infection, and may develop symptoms at any time, the *diagnosis, prophylaxis* and *treatment* of filariasis itself is of importance.

Diagnosis.—The diagnosis of filariasis is made by finding the microfilariæ in the peripheral blood or in the urine or other fluids.

As there is a periodicity in the appearance of the microfilariæ in the peripheral blood, it is advisable to take a drop of blood from the ear at the time the person is in the habit of sleeping. Thus, if he sleeps at night, the microfilariæ are found most numerous in the peripheral blood about midnight; while, if he is habitually sleeping in the daytime, the microfilariæ are most numerous during the period of sleep. The microfilariæ are found in much smaller numbers in the peripheral blood at other times.

If it is not convenient to examine the blood in the fresh condition, or if it is desired to make smears, the thick film method is used: A large drop of blood is placed in the center of the slide and is spread to an area as large as the finger-nail; it is then dried, and the hemoglobin is removed by carefully inverting the dried, unfixed blood-smear in a dish of water, until the hemoglobin is washed out. The smear is then fixed and stained with hematoxylin or with one of the Romanowsky stains.

Frequently the microfilariæ are scarce in the peripheral blood, and it is necessary to examine a larger amount of blood than can be examined in a thick smear. Blood from the ear or finger may be collected in a Wright's tube, allowed to coagulate, and the serum examined. The microfilariæ are numerous in the serum just above the clot and in the serum between the clot and the wall of the tube. The separation of the serum is hastened by centrifuging the blood before or after it has coagulated.

Large amounts of blood may be examined by placing the blood, obtained by puncture of a vein, into sodium citrate solution and centrifuging at high speed. The microfilariæ are collected in clumps and rosettes in the leukocyte layer at the top of the red-cell column. Fülleborn recommends that the blood be placed in several volumes of a solution of 5 per cent. formalin 95 parts, acetic acid 5 parts, and alcoholic solution of gentian violet, 2 parts, and centrifuged. The sediment consists of violet-stained microfilariæ and leukocytes.

Urine and chylous fluids may be centrifuged and the sediment examined.

It is not unusual to fail to find microfilariæ in the blood in elephantiasis. At times, the adult or larvæ worms may be found in the tissues in elephantiasis, but at other times there may be no worms at all.

The blood shows an eosinophilia.

Prophylaxis.—Persons with microfilariæ in the peripheral blood are a source of danger to others, whether or not they have symptoms, and should be required to **sleep under mosquito nets and to take every precaution to avoid infecting mosquitoes.** The failure of the infection to spread from a single case, as shown by Francis for several cities in the southern part of the United States, indicates that there is no danger of spread from a single case, and that mass infection and mass mosquito biting are necessary for the spread of the infection.

Certain drugs kill the microfilariæ in the blood, and this may be of practical use in removing the source of infection; for though the adult worm continues to pass microfilariæ into the circulation, it takes some time for them to accumulate.

As the bite of the mosquito is the only way in which the infection is transmitted to man, every precaution should be taken to **avoid being bitten by mosquitoes in an infected locality. Living in the native quarter of the city should be avoided. Mosquitoes should be destroyed in the usual way; houses should be screened; the people should sleep under mosquito nets**; and, especially where the infection is transmitted by day-biting mosquitoes, **head nets and gloves should be worn; and mosquito repellants may be used.**

Treatment.—No treatment has any effect on the adult worms. As the majority of persons have no symptoms at all, all that can be done is to prevent re-infection and to keep up the general condition until the worms die.

A number of substances kill the microfilariæ, **antimony tartrate** being one of the most active; and Rogers found that **intravenous injections** of safe doses of 1:50 solution of **sodium antimony tartrate** lessened the number of microfilariæ in the peripheral circulation; but it is not known whether it affects the adult worms. Atoxyl has no action; the action of salvarsan is variously reported; McNaughton found that **galyl** kills the microfilariæ.

But the microfilariæ do little or no harm; so, as long as the adult worm is alive, there is little to be gained by treatment that kills the larvæ.

8. *Other Filarial Infections*

Filaria demarquayi, Manson, 1897.—SYNONYM.—*Filaria ozzardi.*

MORPHOLOGY.—The complete female alone is known. The female is white; is 6.5 to 8 centimeters (2 3/5 to 3 1/5 inches) long, and 210 to 250 microns (1/120 to 1/100 inch) in diameter. The vulva is 710 microns (1/35 inch) back of the anterior end, and there are two uterine tubes. The worm is viviparous. There are some differences in structure of the worm in British Guiana (*Filaria ozzardi*) and in the West Indies (*Filaria demarquayi*).

The posterior part is all that is known of the male (*Filaria ozzardi*). This piece is 38 millimeters (1 1/2 inches) long, and 200 microns (1/125 inch) in diameter. The posterior end is curled up, and there are two spicules.

The adult worms are found in the mesentery and under the parietal peritoneum.

Larva.—The larva is 205 microns (1/125 inch) long, and 5 microns (1/5000 inch) in diameter. It has no sheath. There is no periodicity.

Evolution.—Not known. Low and Vincent obtained partial development in *Aëdes calopus;* and Fülleborn obtained partial development in *Anopheles maculipennis.*

PATHOGENIC ACTION.—None.

GEOGRAPHICAL DISTRIBUTION.—The worm is found in some localities in the West Indies and in British Guiana. In some places in Saint Vincent, West Indies, over 26 per cent. of the population are infected.

Filaria (Microfilaria) tucumana.—Only the larva is known. This worm is found in several provinces in Argentina. The larva is 100 to 250 microns (1/250 to 1/100 inch) long, and 3 microns (1/8000 inch) in diameter, and has a sheath. The larvæ are present in the blood throughout the twenty-four hours of the day, but are most numerous at night. In some localities as much as 32 per cent. of the men and over 17 per cent. of the women are infected.

It causes no symptoms.

Filaria (Agamofilaria) conjunctivæ, Addario, 1885.—This worm is found in the eyes of horses and mules in Southeastern Europe and some parts of Asia; and a few cases have been recorded in man. Forbes reports 2 cases from Macedonia, with the finding of the male worm for the first time.

Nothing is known of the life cycle or pathogenic action.

Thelazia pallipæda, Railliet and Henry, 1910.—This is the common eye worm of dogs in Asia; and some cases have been reported in the human. Probably the 3 cases in which worms were removed from the eyes of men in the region of Camp Keithley, in the Philippine Islands, were of this species.

GENUS: LOA STILES, 1905

The characteristics of this genus are the cuticular thickenings over the body, and the large caudal papillæ.

(*i*) *Loasis*

Definition.—Loasis is the name given to the condition resulting from infection with *Loa loa.*

Loa loa, Guyot, 1778.—SYNONYMS.—For the adult worm: *Filaria loa; Filaria oculi.* For the larva: *Filaria diurna; Filaria sanguinis hominis var. major.*

GENERAL CHARACTERISTICS OF LOA LOA.—(*a*) *Morphology of the Adult Worm.*—The adult worm is white in color, and is characterized by the conical anterior end and the cuticular thickenings over the body.

The male is from 30 to 34 millimeters (1 1/5 to 1 2/5 inches) long, and from 350 to 450 microns (1/70 to 1/55 inch) in diameter. The terminal mouth has no lips. The thickest part of the body is just back of the anterior end; and the body gradually tapers to the broadly rounded tail, which is more or less rolled up. There are dewdrop-like cuticular thickenings over the body, except at the anterior end and at times at the posterior end. There are two unequal spicules, three pairs of pre-anal papillæ and two pairs of post-anal papillæ.

The female is 55 to 60 millimeters (2 1/5 to 2 2/5 inches) long, and 450 to 500 microns (1/55 to 1/50 inch) in diameter. The thickest part of the worm is just back of the anterior end; and the rest of the body, being of an even diameter, gives the appearance that has been likened to an olive-tipped sound. The cuticular thickenings cover the body, except at the anterior end; and they are numerous on the posterior end. The vulvar opening is 2.5 millimeters (1/10 inch) back of the anterior end. There is a vagina, into which the two uterine tubes open. The eggs are 50 microns (1/500 inch) by 25 microns (1/1000 inch); and change to straightened-out embryos near the vulva. The worm is viviparous.

(*b*) *Habitat of the Adult.*—The adult worm lives in the connective tissue, and has a predilection for the subcutaneous tissues and the aponeuroses. It travels actively through the tissues, warmth making it more active. There are frequently a number of worms present: in doing a herniotomy, Külz found 7 worms between the skin and the hernial sac; and Penel found 12 males and 22 females in the subcutaneous tissues of one person at postmortem examination. The worms are long lived; and worms have been found traveling in the tissues thirteen years after the person had left the endemic area.

(*c*) *Habitat, Morphology and Biology of the Larva.*—Just as with *Filaria bancrofti,* as the egg passes toward the vulva, the embryo develops and then straightens out, retaining the egg membrane as a sheath.

The microfilariæ, as they circulate in the blood, are 240 to 300 microns (1/100 to 1/80 inch) long, and 6 to 8 microns (1/4000 to 1/3000 inch) in diameter. They resemble the larvæ of *Filaria bancrofti;* and the differential diagnosis is made on a comparison of the nuclear column and the anatomical fixed points or "spots" in the two larvæ.

(*d*) *Periodicity.*—The microfilariæ are numerous in the peripheral blood during the daytime, hence the name *Filaria diurna.* They appear in the blood about 9 or 10 o'clock in the morning; are most numerous about 1 or 2 o'clock in the afternoon; and disappear about 9 or 10 o'clock in the evening. The periodicity of the larva of *Loa loa* cannot be changed like that of the larva of *Filaria bancrofti;* but a prolonged change in sleeping hours may have some effect on the periodicity.

(*e*) *Evolution.*—On account of the diurnal periodicity of the loa larva, Manson suggested that a fly is the transmitter; and he suggested the "mangrove flies," especially *Chrysops dimidiatus.* Leiper showed that the larvæ develop in the salivary glands of *Chrysops dimidiatus* and *Chrysops silacea.*

It is not known how the developed larvæ enter the body of man when the fly bites. The further development of the worm in man is not known, but while still young, the worm moves actively through the tissues. In about a year after infection the worms are nearly full grown; but they are not sexually mature for some time—possibly three or four years later.

Calabar swellings quite frequently appear in persons who have been in the endemic area only two or three months; so it is probable that the worms grow rapidly for a time after being injected into man.

Epidemiology.—The infection is spread from man to man by biting flies belonging to the family Tabanidæ. From Leiper's work, it appears that *Chrysops dimidiatus* and *Chrysops silacea* act as the transmitters. From the limited distribution of the worm, it appears that not many species of flies can act as the transmitter. As far as is known, no other animal than man harbors the worm.

As with other filariæ, the distribution of *Loa loa* is unequal in any region. Thus, in Calabar and in areas in French Equatorial Africa and Kamerun, all the residents are infected; while in other regions, as Togo, there is no infection except in isolated cases. Probably mass infection and mass fly-biting explain this irregular distribution.

Clinical Manifestations.—When the worm travels under the skin there is a peculiar sticking sensation; and when it travels under the conjunctiva there is local itching, pain and irritation, which may be intense. As the worm moves rapidly, the local disturbance lasts only a short time. Elliot reports a case in which there were attacks of neuralgic pain about the ear, the attacks lasting only a few hours.

Calabar swelling is a peculiar, local, transient edema, which occurs on any part of the body, especially the upper extremities: it may occur on the face. Clarac and his co-workers say it never appears on mucous surfaces. With a feeling of tension and heat, and generally with redness, a localized swelling of the skin develops. It is generally sensitive to pressure; and it may be painful. The swelling is 1 to 10 centimeters (2/5 to 4 inches) in diameter, and may be as large as half a goose egg. The swelling seems to be mainly in the subcutaneous tissues, and the overlying skin is tight. There is no fever or other constitutional disturbance.

After two or three days the swelling disappears, but a small nodule may remain in the subcutaneous tissue for a week or two.

When they first begin to appear, the swellings occur frequently, and may occur one after another for several months. They gradually become less frequent, but may continue to recur for years. Natives of the endemic areas claim that they have Calabar swellings only during their youth. The swellings cease, or become less frequent, when the patient goes to a cooler climate.

The worms do no harm other than the local irritation, unless they travel about the glottis, where they may cause edema of the glottis. The Calabar swellings do no harm; and they never suppurate.

Diagnosis.—The methods of finding the larvæ of *Loa loa* in the blood are the same as for finding the larvæ of *Filaria bancrofti,* except that the examination should be made during the daytime.

Calabar swellings frequently occur in persons who do not have microfilariæ in the blood. A history of residence in an endemic area is of importance; and the adult worm will frequently be seen in its travels under the skin and under the conjunctiva. Eosinophilia without other cause, and eosinophilia in the fluid aspirated from the swelling, point to loa infection. Microfilariæ may be numerous in the fluid aspirated from the swelling.

The adult worm, especially when seen about the eye, has to be differentiated from other filariæ; and this is done on a study of the morphology of the worm.

Prophylaxis.—Prophylaxis consists in **the avoidance of bites by flies in the endemic areas.**

Treatment.—The treatment comprises the **operative removal of the worm,** which is quite readily accomplished when the worm is traveling under the skin, and especially under the conjunctiva. As the worm travels rapidly, it is difficult for the patient to get to a physician before the worm disappears; and the physician must work rapidly to secure the worm before it passes on into the deeper tissues.

Elliot took advantage of the worm's liking for warmth, and placed hot fomentations over the eye of the patient. The worm promptly appeared under the conjunctiva. Under cocain, a fold of the conjunctiva, including the worm, was grasped with forceps, and a silk ligature was passed through the fold of the conjunctiva and tied firmly, thus securing the worm. An incision was made in the conjunctiva, and when one end of the worm appeared in the wound it was caught with forceps, and the whole worm was gently drawn out.

No treatment is necessary for Calabar swelling.

Pathogenic Action.—The adult worm lives in the subcutaneous tissues; and, traveling through the tissues, produces a peculiar sticking sensation; or, as when it travels under the conjunctiva, it may produce itching and irritation. The most important action, as it travels under the skin, is the production of transient edemas (Calabar swelling) which may itch intensely. Rubbing the skin favors the production of the swelling, after it has started. Schilling-Torgau and Fülleborn think these swellings are due to products of the worm, which act like various substances that produce a tendency to urticaria.

When the skin is thin, the worm may be seen traveling through the subcutaneous tissues; and it may be well seen when traveling under the ocular conjunctiva or across the bridge of the nose. The worm is very sensitive to heat and cold, coming to the surface and moving actively when the surface is warmed, and retiring to the deeper tissues on the slightest cooling of the surface.

Early in the infection, there is a marked eosinophilia, even as much as 67 per cent.; later the eosinophilia is up to 13 per cent. There is an abundance of eosinophils in the fluid from a Calabar swelling. There is no change in the total leukocyte count; and there is no anemia.

The adult worms may be found in abscesses, or they may die and become calcified.

The larvæ, passed in the connective tissue, reach the circulation through the lymphatics.

Calabar swellings frequently occur in persons who do not have microfilariæ in their blood. The principal explanation for this is that the swellings begin within a few months after infection, and are most frequent in the early period of their appearance, but the worms have not reached sexual maturity at this time. The worms may be all males or all females. But at times a mature worm, containing fully developed embryos, may be found in the tissues, without there being microfilariæ in the blood.

Geographical Distribution.—Loa loa is found only in the tropical portion of West Africa, from Sierra Leone to Angola. It is common along the coast, as well as inland for several hundred miles.

The infection was carried to the West Indies and South America by the slaves; but, as the transmitter was absent, the infection died out.

GENUS: ONCHOCERCA DIESING, 1851

The characteristic of this genus is the barb on the shorter of the two spicules in the male.

(*ii*) *Onchocerciasis*

Definition.—Onchocerciasis is the name given to the condition resulting from infection with *Onchocerca volvulus.*

Onchocerca volvulus, Leuckart, 1893.—SYNONYM.—*Filaria volvulus.*

GENERAL CHARACTERISTICS OF ONCHOCERCA VOLVULUS.—(*a*) *Morphology.*—The adult worm is white in color. The male is 3 to 4 centimeters (1 1/5 to 1 3/5 inches) long, and 130 to 200 microns (1/190 to 1/125 inch) in diameter at the middle, and it tapers markedly toward both ends. The cuticle shows ring-like markings. The mouth is small, and without papillæ. The posterior end is rolled up; there are two unequal spicules, the smaller one with a fish-hook-like barb at the tip. There are two pairs of pre-anal, two pairs of post-anal, and two pairs of caudal papillæ.

The female is from 35 to 40 centimeters (14 to 16 inches) long, and 330 microns (1/75 inch) in diameter at the thickest part. The body tapers toward both ends, with a thickening at the posterior end. The ring-like cuticular thickenings are well developed, and are about 65 microns (1/375 inch) apart. The vulva is from 550 to 750 microns (1/45 to 1/33 inch) back of the anterior end. There is a vagina, into which the two uterine tubes open. The eggs have a peculiar covering, with a twisted prolongation at each end, which has been likened to the tissue paper wrapping on an orange. The worm is viviparous.

(*b*) *Habitat of the Adult.*—The worms are found tangled up in a subcutaneous mass of fibrous tissue, from the size of a pea to that of a pigeon's egg—usually about the size of a hazelnut.

The worms may be numerous: Rodenwaldt found four males and two females in one mass.

(*c*) *Habitat, Morphology, and Biology of the Larva.*—The larvæ are found in the turbid fluid in the spaces in the fibrous mass containing the worms; in the inguinal lymph-glands; and occasionally a few are found in the blood.

The larva is from 240 to 300 microns (1/100 to 1/80 inch) long, and from 6 to 8 microns (1/4000 to 1/3000 inch) in diameter. It has no sheath. In structure it resembles the other microfilariæ.

(*d*) *Evolution.*—The life cycle is not known. Brumpt has suggested that *Glossina palpalis* is the transmitter in Africa. Robles says that the only flies in the endemic zone in Guatemala are *Simulium emboni* and *Simulium dinelli;* and that where the flies are most numerous the cases are most numerous.

The worm grows slowly in man, and the lesions may not appear until six years after the person leaves the endemic area. The tumors may last a lifetime.

Epidemiology.—Nothing is known regarding the spread of the infection. As far as is known, the worm does not occur in any of the lower animals. In Africa, the infection tends to follow the rivers.

Clinical Manifestations.—The constant manifestation is the volvulus tumor. These tumors grow slowly, and are painless, having the appearance of a subcutaneous fibroma. The masses are commonly found over bony prominences, as the trochanter and iliac crest; less commonly over the olecranon and spinous processes of the vertebræ. They are very common on the sides of the thorax. Dubois found the tumors most frequent over the trochanter; next over the iliac crest; and next over the sides of the thorax—these three locations accounting for approximately 79 per cent. of the tumors.

Ouzilleau found that elephantiasis is associated with volvulus infection in Belgian Congo; and Dubois found 48 cases of genital elephantiasis, in 47 of which he found *Onchocerca volvulus.* He found 4 cases of elephantiasis of the foot, and all of the persons were infected with volvulus. The condition is practically the same as elephantiasis due to *Filaria bancrofti.* Dubois says that keratodermia is common in persons with volvulus tumors.

In Guatemala, Robles saw cases of an erysipelatous condition (Erysipelas of the Coast) associated with volvulus tumors—usually on the face. The attack begins with fever of 38.9° to 40° C. (102° to 104° F.), and with swelling, burning and itching of the affected part. The skin shows a greenish discoloration, like that of an old ecchymosis. On removing the volvulus tumor, the condition quickly clears up. In chronic cases, the edema is hard, and the greenish skin becomes furrowed and scaly.

Diagnosis.—The diagnosis is made either by finding the microfilariæ in the fluid aspirated from the tumor or from the inguinal lymph-glands, or by finding the adult worms in the tumor mass.

Prophylaxis.—Nothing is known regarding prophylaxis.

Treatment.—Robles found that injection of **biniodid of mercury into the tumor** kills the worms; but it causes considerable local reaction for a few days.

The most satisfactory treatment is **removal of the tumors**; and this is especially advisable where, as in Guatemala, the tumors are associated with erysipelatous attacks, or where, as in Belgian Congo, the infection is associated with elephantiasis. The tumors are readily removed under local anesthesia.

The erysipelatous attacks and the elephantiasis require the same treatment as given for those conditions under Filariasis.

Pathogenic Action.—At first the worms live in the lymphatics, where they produce a lymphangitis and perilymphangitis. Later, there is formation of fibrous tissue, and the worms lie in a mass of fibrous tissue—the volvulus tumors.

In Belgian Congo, elephantiasis is associated with infection with the worm, probably associated with the lymphangitis caused by the worm. In Guatemala, the volvulus tumors are associated with erysipelatous attacks, probably due to streptococcus infection.

The volvulus tumors are more or less adherent to the overlying skin, and can usually be moved freely over the underlying tissues. The mass never has a capsule. On section, the mass is found to be composed of fibrous tissue and a mass of coiled up worms. The copulatory ends of the worms lie together in the spaces in the mass. In young tumors the spaces contain a semi-transparent, milky fluid, which, after the worms become mature, contains an abundance of microfilariæ. In older tumors, the spaces contain yellowish-gray, slimy material.

The tumors may suppurate, and a living or dead worm may be found in the abscess. Löhlein thinks that the worm may cause muscle abscesses.

The blood shows an eosinophilia, and there is an abundance of eosinophils in the volvulus tumors.

Geographical Distribution.—The worm is found on the west coast of Africa from Sierra Leone to Belgian Congo. In some regions in Belgian Congo, as many as 68 per cent. of the adults and 22 per cent. of the children are infected.

Robles reports that the infection is very common in the region of

Fuego volcano in the western part of Guatemala, and that in some places all of the inhabitants are infected.

On account of the great frequency with which the volvulus tumors occur on the face—99 in 100 times—in Guatemala, Brumpt suggests that this worm is different from the African worm, and suggests the name *Onchocerca caecutiens* for it.

GENUS: ACANTHOCHEILONEMA, COBBOLD, 1870

This genus is characterized by both sexes having two short, conical, lateral appendages near the posterior end. The worms live in the tissues about the serous cavities in primates and carnivora.

Acanthocheilonema perstans, Manson, 1891.—SYNONYM.—*Filaria perstans.*

CHARACTERISTICS OF ACANTHOCHEILONEMA PERSTANS.—(*a*) *Morphology.*—The worms are white; and both sexes are characterized by the mitral like cuticular mass at the tip of the posterior end.

The male is from 4 to 4.5 centimeters (1 3/5) to 1 4/5 inches) long, and from 60 to 80 microns (1/400 to 1/300 inch) in diameter. There are two unequal spicules, four pairs of pre-anal and one pair of post-anal papillæ.

The female is from 7 to 8 centimeters (2 4/5 to 3 1/5 inches) long, and from 120 to 140 microns (1/200 to 1/180 inch) in diameter. The vulva is 600 microns (1/40 inch) behind the anterior end, and there are two uterine tubes.

The adults are found in the connective and fatty tissue at the root of the mesentery, about the descending aorta, about the pancreas and suprarenal glands, and in the pericardial fat.

(*b*) *Larva.*—The larva is 200 microns (1/125 inch) long, and 4.5 microns (1/5500 inch) in diameter. It has no sheath.

The larva shows no periodicity; hence the name—perstans.

(*c*) *Evolution.*—The life cycle is not known. Partial development takes place in *Aëdes argenteus, Taeniorhynchus fuscopennatus, Anopheles maculipennis,* and in a species of *Panoplites.*

The worms are sexually mature in about eighteen months after infection.

EPIDEMIOLOGY.—The mode of transmission is not known.

The infection is unevenly distributed and occurs in irregular areas, as is the case with some other filarial infections. It is common in persons who work in banana groves, and in those who work and live in wooded regions where there is much moisture and the temperature is high. This distribution is evidently connected with the habits of the transmitter.

CLINICAL MANIFESTATIONS.—Generally there are no symptoms. When there are Calabar swellings or abscesses the symptoms are the same as when these conditions are caused by other filariæ.

DIAGNOSIS.—The diagnosis is made by finding the larvæ in the blood.

PROPHYLAXIS.—Nothing is known regarding prophylaxis.

TREATMENT.—None.

PATHOGENIC ACTION.—It appears that *Acanthocheilonema perstans* may cause edemas that are identical with the Calabar swellings caused by *Loa loa.* It is also thought that it causes muscle abscesses. It is thought that it causes filarial fever, with lung symptoms; but it is not clear whether the worm actually plays any part in the condition.

The blood shows an eosinophilia.

GEOGRAPHICAL DISTRIBUTION.—The worm is widely distributed in tropical Africa; it is also present in British Guiana.

GENUS: DIROFILARIA RAILLIET AND HENRY, 1911

The adult worms live in the cavities of the heart.

Dirofilaria magalhæsi, R. Blanchard, 1895.—The adult worms were found in the left ventricle of the heart of a child in Rio de Janeiro, in 1887.

CHARACTERISTICS OF DIROFILARIA MAGALHÆSI.—The worms are white in color; the anterior end is enlarged; and the cuticle is transversely striated.

The male is 8.3 centimeters (3 1/3 inches) long, and 400 microns (1/60 inch) in diameter. The posterior end is curled up. There are two unequal spicules; four pairs of pre-anal, and three pairs of post-anal papillæ.

The female is 15.5 centimeters (6 1/5 inches) long, and 715 microns (1/35 inch) in diameter. The vulva is 2.56 millimeters (1/10 inch) from the anterior end. The eggs are 38 microns (1/660 inch) by 14 microns (1/1780 inch). The worm is viviparous.

Nothing is known of the life cycle or pathogenic action of the worm.

Dirofilaria immitis.—The adult worms are found in the cavities of the right side of the heart in dogs, wolves, and foxes.

CHARACTERISTICS OF DIROFILARIA IMMITIS.—(*a*) *Morphology.*—The male is 12 to 18 centimeters (4 4/5 to 7 1/5 inches) long, and 700 to 900 microns (1/35 to 1/28 inch) in diameter.

The female is 25 to 30 centimeters (10 to 12 inches) long, and 1 to 1.3 millimeter (1/25 to 1/20 inch) in diameter. The vulva is 7 millimeters (7/25 inch) back of the anterior end.

The larva is 285 to 295 microns (1/88 to 1/85 inch) long, and 5 microns (1/5000 inch) in diameter. It has no sheath.

The larvæ appear in the blood of the dog at night.

(*b*) *Evolution.*—A mosquito is the transmitter. The larvæ develop in the malpighian tubules of the mosquito, pass forward to the labium, and escape through Dutton's membrane, when the mosquito bites, and pass through the skin of the dog, just as the developed larva of *Filaria bancrofti* passes through the skin of man.

PATHOGENIC ACTION.—It has been suggested that the worm may infect man; but no cases of infection are actually known.

C. NEMATODES IN THE SUBCUTANEOUS TISSUES, THE EMBRYOS NOT PASSING INTO THE BLOOD

Some nematodes have been found in the subcutaneous tissues as erratic parasites, as *Gnathostomum spinigerum* and *Rhabditis niellyi*. *Dracunculus medinensis* is the only nematode in which the adult is a typical parasite of the subcutaneous tissues.

GENUS: DRACUNCULUS KNIPHOFF, 1759

In this genus, the vulvar opening is so close to the anterior end that there does not appear to be any vulvar opening in the gravid female, the larvæ appearing to escape by the mouth.

(*iii*) *Dracontiasis*

Definition.—Dracontiasis is the name given to the condition resulting from infection with *Dracunculus medinensis.*

Dracunculus medinensis, Velsch, 1674.—SYNONYMS.—*Filaria medinensis; Guinea worm; Medina worm.*

CHARACTERISTICS OF DRACUNCULUS MEDINENSIS.—(*a*) *Morphology.*—The male worm is known only from Leiper's experimental infections of monkeys, where, six months after infection, Daniels found two males and two females that had not reached sexual maturity. The males were 22 millimeters (7/8 inch) long, and had five pairs of postanal papillæ.

The female is white in color; is 32.5 to 120 centimeters (13 to 48 inches)—generally about 90 centimeters (36 inches) long, and 1.5 to 1.7 millimeters (1/17 to 1/15 inch) in diameter. The anterior end is bluntly rounded; the mouth is triangular, and opens in the center of an elevation which is surrounded by six papillæ. The vulvar opening is just back of these papillæ. The posterior end terminates in a hook-shaped cuticular thickening. After fertilization the uterus is packed with developing embryos; the intestinal tract atrophies; and the worm becomes a long tube filled with embryos.

(*b*) *Larva.*—The larva is 500 to 750 microns (1/50 to 1/33 inch) long, and 15 to 25 microns (1/1660 to 1/1000 inch) in diameter. It has no sheath. The body is flattened dorsoventrally, and nearly one-third of the length of the larva is made up of the slender, pointed tail. The larva is much more developed than are the larvæ of the other filariæ at the time they are passed from the female worm.

(*c*) *Evolution.*—The larvæ, passed into fresh water, swim actively about in search of a host. If they do not find a host, they sink to the bottom and die in from three to six days. They are killed by drying; but there are reports of the larvæ recovering motility after drying for from twelve to twenty-four hours.

The intermediate host is various species of cyclops. The larva enters the cyclops through the mouth, passes to the intestine, and from there to the body cavity, where it undergoes development. It loses the pointed tail and becomes larger; and in five weeks the development in the cyclops is completed.

When water, containing cyclops with developed medinensis larvæ, is taken into the stomach of man, the hydrochloric acid in the gastric juice kills the cyclops; but it makes the medinensis larvæ move actively.

The development from here is not well known; but it is probable that the larvæ bore their way through the stomach wall. The worms live in the connective tissue about the root of the mesentery (or possibly in the peritoneal cavity) until the female is fertilized. The male then dies, and the female travels to the subcutaneous tissues. Directed by a special chemotactic action, the female travels to a part of the body where there is opportunity for her to pass her larvæ into water. Arriving at the desired place in the subcutaneous tissues, the worm coils up, the skin over the anterior end of the worm breaks, and when the infected person enters the water, or water is poured on the skin in the neighborhood of the worm, a number of larvæ are passed into the water.

The time from infection to the appearance of the worm under the skin, ready to pass the larvæ, is from nine months to a year.

Epidemiology.—The infection is spread by drinking water containing cyclops infected with medinensis larvæ.

The opinion still exists that the larvæ may pass through the skin; but the weight of opinion is that the only way in which the larvæ enter the body of man is through the mouth.

The infection occurs in lower animals, as dogs, horses, cattle, monkeys, jackals, and leopards.

Symptomatology.—There are no symptoms until the worm reaches the place under the skin through which the larvæ are to be passed, and coils up. The skin over the involved area begins to itch, and a furuncle-like swelling, as large as a pigeon's egg, develops. It may be possible to see the outline of the coiled-up worm through the skin. There may be some pain at the site of the lesion; and there may be urticaria and fever. At the summit of the swelling a vesicle forms; at first with clear fluid, which later becomes turbid. When the vesicle breaks, it uncovers an opening in the skin, through which the worm discharges the larvæ; and, after discharging some of the larvæ, the anterior end of the worm protrudes through the opening.

The larvæ are discharged in two or three weeks, and then the worm is readily extracted; or, if it remains in the tissues, it is absorbed, or it calcifies. The wound heals quickly.

If the worm is broken in attempts at extraction, or if the wound becomes infected, as from scratching, an abscess or a phlegmon may form. Calcified remains of the worms may be the center of inflammatory reaction months or years after the death of the worm.

The common site for the lesions is about the feet and ankles; 50 to 65 per cent. about the feet and ankles, and 20 to 23 per cent. in the legs—92 per cent. in the lower limbs. The lesion may occur on any part of the body, even under the tongue. There is commonly one worm; but there may be as many as 20, or even 50.

Diagnosis.—The diagnosis is readily made from the appearance of the lesion; though there may be confusion if the lesion is in an unusual location. The urticaria and the eosinophilia may be of assistance. The *x*-ray will show calcified worms; and it may show the living, coiled-up worm.

Prophylaxis.—Prophylaxis consists in **avoiding the drinking of contaminated water.** Water from infected wells can be chemically treated or boiled. Leiper has devised a method of killing cyclops in wells by passing steam through the water in the well.

Treatment.—The best plan is to **douche the skin over the wound with water**, until the worm has discharged all of the larvæ. Then the **worm can be extracted by careful traction** on the protruding end of the worm. Until the worm has discharged all larvæ, traction may result in rupture of the worm and lead to local inflammation and abscess formation.

A 1:1000 solution of **bichlorid of mercury** may be injected into the folds of the worm; but this causes some inflammatory reaction. **Chloroform, cocain solution, and tincture of iodin** are also used for injection into the worm through the opening in the skin.

Macfie reports good results from the intravenous injection of one grain doses of tartar emetic every other day for six to nine doses. Good results have been reported from the intravenous injection of neo-arsphenamin.

When the wound suppurates, it is treated as an ordinary suppurating wound.

Mechanism and Pathogenic Action.—In traveling to the proper place to deposit the larvæ in water, the female worm is unerringly guided. If the person wades in water the worm goes to his feet and ankles; if he carries water in a goat-skin on his back, the worm goes to his back; if he carries water on his head, the worm goes to the skin of his head and neck.

When the female coils up in the subcutaneous tissues, she pierces the dermis; and a bleb forms on the skin; and, on opening this bleb, the anterior end of the worm is found lying in an opening in the skin.

When water is placed on the skin around this opening, a hyaline, cylindrical mass, 2 to 3 centimeters (4/5 to 1 1/5 inches) long, and 1 millimeter (1/25 inch) in diameter, protrudes from the mouth of the worm, and ruptures, setting free a turbid fluid. This cylindrical mass is a hernia of a part of the uterus, and the turbid fluid swarms with larvæ. The sac is protruded through the mouth, or through the vulvar opening which is so close to the mouth that the sac appears to come from the mouth. The worm does not risk all of the larvæ to one exposure of water; but she can be made to repeat the protrusion of the sac of larvæ at intervals of one or two hours.

If left undisturbed, the worm empties all of her larvæ, by passing out a portion of them whenever water comes in contact with the skin where she lies. Then the worm dies, and is readily removed, or is absorbed; or it may calcify. At times, especially when there are attempts at extraction, the tissues around the worm become infected with bacteria, and an abscess forms. Suppuration kills the larvæ.

It is probable that the bleb on the epidermis is caused by a substance excreted by the worm; and the marked tissue reaction that occurs when the worm is broken in the tissues, as in attempts at extraction, is probably due to some substance from the worm. At times there is urticaria and fever, probably due to some substance excreted by the worm. The blood shows an eosinophilia up to 13 per cent.

Geographical Distribution.—The worm has been known since ancient times in Asia Minor, Arabia, Persia, Turkestan, and a part of India; and it is probably the Fiery Serpent that harassed the Israelites in the desert. It is very common in a section of Africa from about 15° north to the equator, extending entirely across the continent from Senegal to Abyssinia; and in some places nearly all of the inhabitants have the infection.

The infection was carried to America by the slaves, and has become endemic in the region of Bahia, Brazil, in Curaçao, and in British Guiana.

D. NEMATODES IN THE LUNGS

Nematodes are common in the lungs of domestic animals, but are rare in the human.

GENUS: METASTRONGYLUS MOLIN, 1861

This genus lives in the bronchi of pigs, and has been found in man.

Metastrongylus elongatus, Dujardin, 1845.—The male is 12 to 25 millimeters (½ to 1 inch) long; the female is 20 to 50 millimeters (4/5 to 2 inches) long. The eggs are 57 to 100 microns (1/440 to 1/250 inch) long and 39 to 72 microns (1/640 to 1/340 inch) in diameter. The worms live in the medium-sized bronchi in the pig, and may cause severe verminous bronchitis. The worm has been found in the lungs of a child, and once in the intestine of an adult who handled pork.

E. NEMATODES OF THE KIDNEYS

Dioctophyme renale, Goeze, 1782.—SYNONYM.—*Eustrongylus visceralis.*—The worms are red in color. The male is from 14 to 40 centimeters (5 3/5 to 15 3/4 inches) long, and from 4 to 6 millimeters (1/6 to 1/4 inch) in diameter. The female is from 20 centimeters to 1 meter (8 to 39 inches) long, and from 5 to 12 millimeters (1/5 to 1/2 inch) in diameter. The eggs are from 64 to 68 microns (1/390 to 1/370 inch) long, and from 40 to 44 microns (1/625 to 1/570 inch) in diameter.

The worms live in the kidney of various mammals in all parts of the world. They are very common in Italy. At first the worms live in the pelvis of the kidney; but they destroy the kidney tissue gradually, and come to lie in the fibrous capsule. At times the worms are free in the peritoneal cavity, and there is no evidence of lesions in the kidneys, as in one case seen by the writer in Washington. Wislocki examined 3,200 dogs in the District of Columbia and neighboring states, and found 12 infected with the worm. In every case the worms were free in the peritoneal cavity.

A few cases of infection have been reported in man.

The life cycle is not known.

II. ACANTHOCEPHALA

The ~~spine-headed worms~~ have no digestive tract; they have a retractile beak provided with hooks; the body shows transverse ridges, but this does not correspond to internal segmentation. The egg has three envelopes and contains an embryo with hooklets. The larva is parasitic in insects, crustaceans, fish, and small mammals. The adult lives in the digestive tract—generally the small intestine—of vertebrates.

GENUS: GIGANTORHYNCHUS, HAMANN, 1892

Gigantorhynchus gigas, Goeze, 1782.—The male is 5 to 10 centimeters (2 to 4 inches) long and 3 to 5 millimeters (1/8 to 1/5 inch) in diameter; the female is 20 to 35 centimeters (8 to 14 inches) long and 4 to 10 millimeters (1/6 to 2/5 inch) in diameter. The beak is large—hence the name of the worm. The adult worm lives in the small intestine of the pig; and it is said to be common in man on the banks of the Volga, in Russia. The larva stage is passed in a grub worm (canker worm) and in a beetle.

Gigantorhynchus moniliformis, Bremser, 1811.—The male is 4 to 5 centimeters (1 3/5 to 2 inches) long; the female 7 to 10 centimeters (2 4/5 to 4 inches) long. The worm is found in the intestine of rats, and has been found in man. Cockroaches and beetles are the intermediate hosts.

III. GORDIACEA

The hair worms have an intestinal tract in the larval stage; but the intestinal tract is atrophied in the adult. The adults live in brooks, coiled up in a ball of a number of worms—"gordian knot."

The *evolution* is complicated, and usually involves two hosts: first an insect, and then a fish. The worms may be taken in by man, and live in the intestine for some time: in one case, five months; in another case, nine months. They have no pathogenic action.

It is probable that these worms furnish the basis for the popular idea that a hair will develop into a worm.

CLASSIFICATION OF OVA OF NEMATHELMINTHES
(Modified from Brumpt)

					Dimensions in Microns	
Nematoda	Ova with a single envelope	Wall smooth	Thick	Bulging on one side, flat on the other	50 x 23	*Oxyuris vermicularis**
				Regular ovoid	57 x 39	*Physaloptera caucasica*
				Clear plug at each pole	55 x 25	*Trichuris trichiura*
			Transparent	2 to 4 blastomeres	60 x 40	*Ancylostomum duodenale*
				....	60 x 40	*Ternidens deminutus*
				2 to 4 blastomeres	70 x 40	*Necator americanus*
				4 to 8 blastomeres	70 x 40	*Oesophagostomum brumpti*
				8 to 32 blastomeres	80 x 48	*Hœmonchus contortus*
					80 x 45	*Trichostrongylus probolurus*
					83 x 45	*Trichostrongylus instabilis*
					87 x 48	*Trichostrongylus vitrinus*
				Thick embryo, folded in two	54 x 32	*Strongyloides stercoralis*
				Thin, twisted embryo	80 x 55	*Metastrongylus apri*
		Wall ornamented		Mammellated, brown	60 x 44	*Ascaris lumbricoides*
				Regularly cribbed, with depressions, yellow	75 x 65	*Toxascaris limbata*
				Cribbed with depressions, except at the poles, brown	66 x 42	*Dioctophyme renale*
Acanthocephala	Ova with three envelopes; embryo with rows of spines			Ova have shallow lozenge-shaped depressions	85 x 45	*Gigantorhynchus gigas*
					100 x 50	*Gigantorhynchus moniliformis*

*Ones underscored are the ones normally parasitic in man.

REFERENCES

General

BRUMPT, E. Précis de parasitologie. 1913, 2d Ed., Masson & Co., Paris.

CASTELLANI, A., AND CHALMERS, A. J. Manual of tropical medicine. 1919, 3d Ed., Baillière Tindall & Co., London.

CHANDLER, A. C. Animal parasites and human disease. 1918, John Wiley & Sons, New York.

TROPICAL DISEASES BULLETIN. Tropical Diseases Bureau, Hospital for Tropical Diseases, Endsleigh Gardens, Euston Road, London, N. W. 1. (Excellent abstracts of all literature on Helminthiasis.)

Ascariasis

AVILES, J. The rôle of ascariasis in gall-bladder disease. Surg., Gynec. and Obst., Chicago, 1918, xxvii, 459.

COUTANT, A. F. Chenopodium poisoning: Report of a case. Jour. Am. Med. Assn., Chicago, 1916, lxvii, 1599.

DARLING, S. T., BARBER, M. A., AND HACKER, H. P. Treatment of hookworm infection. Jour. Am. Med. Assn., Chicago, 1918, lxx, 499.

DEADERICK, W. H., AND THOMPSON, L. The endemic diseases of the southern states. 1916, W. B. Saunders Company, Philadelphia.

GONZAGA, L. Tratamento da lumbricose na infancia. Brazil-med., Rio de Janeiro, 1918, xxxii, 310.

HALL, M. C. The longevity of adult ascarids outside the body of the host. Its bearing on anthelmintic treatment. Jour. Am. Med. Assn., Chicago, 1917, lxviii, 772.

HALL, M. C., AND FOSTER, W. D. Oil of chenopodium and chloroform as anthelmintics. Jour. Am. Med. Assn., Chicago, 1917, lxviii, 1961.

LUCKE, B. Statistical study of the prevalence of intestinal worms in 35,000 white and colored troops at Camp Zachary Taylor, Kentucky. Mil. Surgeon, Washington, 1919, xliv, 620.

MONTEL, M. C. R. Erythème noueux et ascaridiose intestinale. Bull. Soc. méd. chir. de l'Indochine, Saigon, 1916, vii, 48.

PANTIN, M. Life-history of Ascaris lumbricoides. Brit. Med. Jour., London, 1918, ii, 287.

RANSOM, B. H. A newly recognized cause of pulmonary disease—Ascaris lumbricoides. Jour. Am. Med. Assn., Chicago, 1919, lxxiii, 1210.

RANSOM, B. H., AND FOSTER, W. D. Life history of Ascaris lumbricoides and related forms. Jour. Agric. Research, Washington, 1917, xi, 395.

——— Recent discoveries concerning the life history of Ascaris lumbricoides. Jour. Parasitology, Urbana, Ill., 1919, v, 93.

SALANT, W. The pharmacology of the oil of chenopodium. Jour. Am. Med. Assn., Chicago, 1917, lxix, 2016.

SCHWARTZ, B. A blood-destroying substance in Ascaris lumbricoides. Jour. Agric. Research, Washington, 1919, xvi, 253.

SHIMAMUTRA, T., AND FUJII, H. "Askaron" a toxin extracted from Ascaris lumbricoides. Saikingaku Zasshi, 1916, June 10 and July 19, pp. 25 and 9. (Review by R. G. MILLS, China Med. Jour., 1917, xxxi, 69 and 76.) (Abstracted in Trop. Dis. Bull., 1917, x, 117.)

STEWART, F. H. On the life history of Ascaris lumbricoides. Brit. Med. Jour., London, 1916, ii, 5.

——— Recent experiments on the life history of Ascaris lumbricoides. Brit. Med. Jour., London, 1919, i, 102.

YOSHIDA, S. On the development of Ascaris lumbricoides. Jour. Parasitol., Urbana, Ill., 1919, v, 105.

Yoshida, S., and Hotta. Resistance of Ascaris eggs. Japan Med. World, Aug. 31, 1919, 198. (Abstr. Journ. Am. Med. Assn., 1919, lxxiii, 1246).

Oxyuriasis

Wood, W. A. Appendicopathia oxyurica. Med. Jour. Australia, Sidney, 1918, i, 234.

Trichuriasis

DeVézeaux de Lavergne. Récherches sur le parasitisme intestinal des troupes en campagne. Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, 3e Ser., xxxiv, 95.

Montoya, T. W. Papel patogéno de Tricocéfalo. Rev. clin. Medellin, Colombia, 1918, ii, 353.

Trichiniasis

Booth, B. A., Goehring, W. N., and Kahn, M. Note on the treatment of trichinosis with thymol. Jour. Am. Med. Assn., Chicago, 1916, lxvii, 2000.

Flury, F. Beiträge zur Chemie und Toxicologie der Trichinen. Arch. f. exper. Path. u. Pharmakol., Leipzig, 1913, lxxiii, 164.

Lintz, W. Trichinosis and the cerebrospinal fluid. Jour. Am. Med. Assn., Chicago, 1916, lxvi, 1856.

Ransom, B. H. Trichinosis. Report of the Eighteenth Annual Meeting of the United States Live Stock Sanitary Association, Chicago, Feb. 16-18, 1915, p. 147.

——— Effects of refrigeration upon larvæ of Trichina spiralis. Jour. Agric. Research, Washington, 1916, v, 819.

Schwartz, B. Serum therapy for trichinosis. Jour. Am. Med. Assn., Chicago, 1917, lxix, 884.

——— Observations and experiments on intestinal trichinæ. Jour. Agric. Research, Washington, 1918, xv, 467.

Stäubli, C. Trichinose. Handbuch der pathogenen Mikroörganismen. Kolle und Wassermann, 1913, Zweite Auflage, viii, 73. Gustav Fischer, Jena. (With Bibliography.)

Gnathostomum

Samy, P. C. Gnathostomum siamense or Gnathostoma spinigerum Owen. Indian Med. Gaz., Calcutta, 1918, liii, 436.

Filariasis

Clarac, A., Leboeuf and Rigollet. Microfilarioses et filarioses. Grall et Clarac's Traité du pathologie exotique, clinique et therapeutique. 1913, vi, 285. J. B. Baillière et Fils, Paris.

Francis, E. Filariasis in the southern United States. Bull. No. 117, Hyg. Lab., Washington, 1919.

Fülleborn. Die Filarien des Menschen. Kolle und Wassermann's Handbuch der pathogenen Mikroörganismen. 1913, Zweite Auflage, viii, 185. Gustav Fischer, Jena.

Johnson, F. B. Filarial infection. An investigation of its prevalence in Charleston, S. C. South. Med. Jour., Birmingham, Ala., 1915, viii, 630.

Loa Loa

Elliot, R. H. Removal of worm (Filaria loa) from the eye. Brit. Med. Jour., London, 1918, i, 502 and 604.

Onchocerca volvulus

Calderon, V. M. Enfermedad nueva en Guatemala. Juventud méd., Guatemala, 1917, xvii, 97. (Report of Dr. R. Robles' paper.)

Dracunculus medinensis

Macfie, J. W. S. Intravenous injection of tartar emetic in guinea-worm infection. Lancet, London, 1920, i, 654.

CHAPTER XLVIII

DISEASES CAUSED BY ARTHROPODS

By Eugene R. Whitmore, M.D.

Phylum: Arthropoda, p. 226:—A. Class Crustacea, p. 226.
B. Class Arachnidia, p. 227: Order Pentastomida, p. 227: Porocephaliasis, p. 227—Order Acarina, p. 228: Acariasis, p. 228: Demodectic acariasis, p. 228; Sarcoptic acariasis, p. 229:—Etiology, p. 229; Symptomatology, p. 229; Diagnosis, p. 230; Prophylaxis, p. 230; Treatment, p. 230; Prognosis, p. 231; Pathology, p. 231—Acarodermatitis urticarioides, p. 231:—Geographical distribution and history, p. 231; Etiology, p. 232; Symptomatology, p. 232; Diagnosis, p. 233; Treatment, p. 233—Other forms of acariasis, p. 233:—Trombidiidæ, p. 234; Treatment, p. 234—Ixodiasis, p. 235:—Evolution, p. 235—Tick bite, p. 236; Tick paralysis, p. 237:—Mechanism of process, p. 237; Immunity, p. 238; Symptomatology, p. 238; Treatment, p. 238—Transmission of pathogenic microörganisms, p. 239—Order Scorpionidea, p. 239—Order Araneida, p. 240:—Symptoms and treatment, p. 240.
C. Class Myriapoda, p. 241.
D. Class Insecta, p. 241:—Complete metamorphosis, p. 241; Incomplete metamorphosis, p. 242—Order Hemiptera, p. 242:—Suborder Aptera, p. 242:—Pediculosis, p. 242:—Symptomatology, p. 243; Diagnosis, p. 243; Treatment, p. 244—Suborder Heteroptera, p. 244:—Cimicidæ, p. 244; Reduviidæ, p. 246—Order Hymenoptera, p. 247:—Apidæ, p. 247; Formicidæ, p. 247—Order Coleoptera, p. 248; Order Lepidoptera, p. 248:—Treatment, p. 249—Order Orthoptera, p. 249; Order Diptera, p. 249:—Suborder Aphaniptera, p. 249:—Pulicidæ, p. 250; Sarcopsyllidæ, p. 252—Suborder Brachycera, p. 254:—Tabanidæ, p. 254; Syrphidæ, p. 254; Sepsidæ, p. 254; Muscidæ, p. 255; Anthomyiidæ, p. 261; Phoridæ, p. 261; Sarcophagidæ, p. 261; Oestridæ, p. 262; Pathogenic action of fly-larvæ, p. 263:—Cutaneous myiasis, p. 263:—Larva migrans, p. 264; Phantom tumors, p. 264; Furunculous myiasis, p. 264—Myiasis of cavities, p. 264; Intestinal myiasis, p. 265—Suborder Nematocera, p. 268:—Simulidæ, p. 268; Chironimidæ, p. 268; Psychodidæ, p. 269; Culicidæ, p. 269.

Arthropods have been associated with man as parasites for centuries, and we have record of lice leaving no less a personage than a king when he was dying. We have record of their noxious action in the plagues of lice, flies and locusts which were sent upon the Egyptians in the time of Moses. But up to about forty years ago, other than the annoyance produced by them and the causation of a few diseases, very little was known regarding the actual connection of arthropods with disease, although Beauperthuy, in 1853, suggested that flies and mosquitoes transmitted disease. In 1879, Manson demonstrated the rôle of mosquitoes in the transmission of filariasis, and since that time arthropods have been shown to play a part in the transmission of a number of diseases.

Arthropods may be *accidental parasites* of man, as, for instance, the fly larvæ which get into the intestinal tract. Or they may be *discretionary parasites,* such as bedbugs and mosquitoes, which live about the habitations of man, and bite man and the lower animals more or less regularly. They may be *obligatory parasites,* as the itch mites and blood-sucking lice, which are adapted to a particular host, and must feed regularly.

Arthropods may cause disease by their own presence on or in the body, as in scabies, prediculosis and myiasis. But the greatest importance of the arthropods is their action as carriers of disease-producing organisms. The organisms may be carried mechanically—*mechanical transmission*—as the house-fly carries the typhoid bacillus on its legs or in its digestive tract, or by the slightly greater adaptation in which the flea sucks blood containing the plague bacillus, its digestive tract acting as an incubator for the plague bacillus: the bacillus multiplies and is injected into a new host when the flea bites again. Or the organisms may go through a cycle of development in the body of the arthropod host—*biological transmission*—as in the case of the malarial fever parasite.

PHYLUM: ARTHROPODA

The arthropods are bilaterally symmetrical animals, with the body formed of more or less differentiated segments. They have a chitinous exoskeleton, and have articulated appendages.

Of the six classes, two (*Arachnidia* and *Insecta*) contain parasites of man. The *Crustacea* are never parasitic in man, but cyclops and several species of crabs serve as the intermediate host for certain worms that are parasitic in man. Of the *Myripoda,* the centipedes have a venomous sting.

A. CLASS: CRUSTACEA

The crustacea have two pairs of antennæ; they live in water, and breathe by means of *gills.* This class includes cyclops, crabs, shrimps and lobsters. In some persons, eating crabs, shrimps, or lobsters will cause urticaria.

Several species of cyclops serve as the intermediate host of the guinea-worm (Dracunculus medinensis), and several species of crabs serve as the intermediate host of *Schistosoma japonicum.*

B. CLASS: ARACHNIDIA

The arachnidia have no antennæ; they live on land, and breathe through the cuticle or by means of tracheæ. There are two parts to the body: the cephalothorax, and the abdomen, the cephalothorax being formed by a fusion of the segments of the head and thorax. The cephalothorax bears the mouth-parts and the legs.

The arachnidia include a large number of orders; but only two orders (*Pentastomida* and *Acarina*) contain organisms which are strictly parasitic for man. The *Scorpionidea* (scorpions) and *Araneida* (spiders) have a venomous sting or bite.

I. Order: Pentastomida

Of the Pentastomida, the *Linguatulidæ* or *tongue-worms* are parasitic in the respiratory tract of mammals (*Linguatula*) and reptiles (*Porocephalus*). The larva lives in the viscera of various animals, especially mammals, the larva of linguatula being fairly common in the peritoneal cavity of man. The larva of porocephalus is common in the liver or peritoneal cavity of monkeys.

Infection with the Pentastomidæ is known as:

(1) Porocephaliasis

Synonyms.—Tongue-worm infection.

Linguatula serrata (Frölich, 1879) is found in Europe and America. The adults live in the nasal fossæ of dogs, while the larvæ are encysted in the viscera (especially the liver and lungs) of rabbits, cattle and sheep. Both the larva and the adult have been found in man in Europe. The eggs, containing a four-legged embryo, are found in the nasal secretions. The larvæ cause no symptoms, and are found at postmortem examination.

Porocephalus armillatus (Wyman, 1847) is found in Africa. The adults live in the lungs of the python and other snakes, and the larva is found in the peritoneal cavity or liver of rodents and monkeys. The larva is not infrequently found in the viscera of man at postmortem examination.

Porocephalus moniliformis (Diesing, 1836) is found in Africa in the same animals in which Porocephalus armillatus is found, and some authorities hold that the two organisms are the same. The larvæ are not infrequently found in the viscera of man at postmortem examination. Seiffert found them in 17 of 218 postmortem examinations in Kamerun in 1910. They cause no symptoms, unless they are located where they will do harm mechanically. Raebiger reports a case of chronic internal hemorrhagic pachymeningitis, which he thinks due to the larvæ found in the frontal sinuses (Stirnhöhlen) or in the anterior cranial fossæ. The patient died of pneumonia, and three larvæ were found in the bronchi of the pneumonic lung; Raebiger thinks that the pneumonia was possibly due to the larvæ.

The African natives not infrequently eat the flesh of snakes, and it is probable that the eggs of Porocephalus are taken into the digestive tract in this way.

II. Order: Acarina

In the Acarina the body is globular and the cephalothorax and abdomen are fused. The larva has three pairs of legs; the nymph and the adult have four pairs of legs. There are organs of fixation, as hairs, hooklets or suckers, on the ends of the legs.

The mouth-parts make up the rostrum which is lodged in a depression, the camerostome. The labium and maxillæ are fused to form the hypostome; above is a pair of mandibles; and the upper border of the camerostome may be prolonged forward to form an epistome. At the base of the rostrum, on either side, is inserted a maxillary palp. The salivary glands open at the base of the hypostome, and the irritating saliva is poured directly into the wound when the parasite bites.

The sexes are separate, the males being smaller than the females.

The Acarina commonly live free, but there is a tendency for them to become parasitic. Infection with Acarina is known as:

(1) Acariasis

(a) Demodectic Acariasis

The *Demodicidæ* are vermiform, have no tracheæ, the four pairs of legs are three-jointed, and are articulated on an epimerite. The mandibles are styliform, and the palps are hooked.

Demodex folliculorum lives in the sebaceous glands and hair follicles of the skin. It is quite common in the sebaceous material, especially about the alæ of the nose, more commonly in persons with thick, oily skin. The adult is from 300 to 380 microns (1/83 to 1/66 inch) long, and from 40 to 45 microns (1/615 to 1/555 inch) in diameter. The eggs are passed in the sebaceous material; a six-legged larva hatches from the egg; this changes to an eight-legged nymph which molts twice to become the adult.

Ordinarily Demodex causes no disturbances in man; but it has been considered to be the cause of a slight pigmentation of the skin similar to tænia versicolor, with slight scaliness of the skin in the affected areas. It has been suggested that it is connected in a causal way with acne. It has been suggested that Demodex may act as a transmitter of various pathogenic microörganisms, especially the leprosy bacillus; but nothing definite is known regarding it.

In lower animals, as dogs, Demodex causes a follicular type of itch, which is very resistant to treatment.

No treatment seems to be successful in removing the parasites.

(b) *Sarcoptic Acariasis*

Synonyms.—Scabies, itch, army itch, Hungarian itch, Italian itch, Polish itch.

The *Sarcoptidæ* are globular in form; they have no tracheæ; the palps are adherent, have three joints, and are not armed. The mandibles are scissors-like. The legs are articulated on an epimerite. The larva has six legs; the nymph and adult have eight legs.

There are two genera: *Sarcoptes* and *Psoroptes*. The Sarcoptes burrow in the epidermis and deposit their eggs in the burrow; the Psoroptes deposit their eggs at the base of the hairs, and the epidermis piles up in scales.

Etiology.—*Sarcoptes scabiei* is the common itch mite. The adults are yellowish-white in color, slightly oval in shape, and the tegument is marked by transverse parallel folds, interrupted on the dorsal surface by two transverse rows of short spines. On the dorsal surface, in the anterior part, on either side, are three larger heavy spines; and in the posterior part, on either side, are seven heavy spines, bifurcated at the tip, arranged in two longitudinal rows.

The female is from 330 to 459 microns (1/75 to 1/55 inch) long, and from 250 to 350 microns (1/100 to 1/70 inch) broad. The first and second pairs of legs are terminated by a sucker and hairs; the third and fourth pairs of legs are terminated by hairs. The male is from 200 to 235 microns (1/100 to 1/70 inch) long, and from 145 to 190 microns (1/170 to 1/130 inch) broad. The first, second and fourth pairs of legs are terminated by a sucker.

The female lives in a burrow in the epidermis, and the male lives in the burrow or beside the burrow under the epidermis. The female passes an egg, and the embryo develops as the egg passes out of the burrow. At the end of seven days the six-legged larva hatches and lives on the surface of the skin. At the end of sixteen days the eight-legged nymph is developed and lives in the crusts on the skin. At the end of twenty-eight days, the adult male and female are developed and copulate; the female develops a new orifice for the passage of the eggs, burrows into the skin, and starts depositing her eggs. The male dies shortly after copulation; the female dies after depositing the eggs.

EPIDEMIOLOGY.—The infection is readily spread from person to person. The infection is most commonly contracted by sleeping with an infected person, or by sleeping in a bed in which an infected person has slept, if the bed-linen has not been changed. Less commonly it is contracted by shaking hands with an infected person, and by the common use of towels, toilet articles, or tools. Intimate contact, as in barracks and camps, favors the spread of the infection.

Symptomatology.—The condition begins with itching, usually intense, caused by the mites burrowing in the epidermis. As warmth seems to make the mite more active, the itching is more severe at night, and is increased by heat or exercise.

The burrows appear as straight or tortuous, grayish to blackish lines; and the papules, vesicles, and pustules complete the picture. The lesions are found especially in the fold between the fingers, on the wrists, about the elbow, axilla, feet and ankles, inner side of the thighs, and about the genitalia and on the lower part of the abdomen. Stiles refers to the great frequency of the lesions about the penis in men, and about the nipple in women.

The severity and extent of the lesions depend upon the length of time the disease has existed, the habits as to cleanliness of the patient, and to some extent upon the irritability of the skin. In some cases there may be an eczematous condition. In other cases there may be crust formation, with callous thickening of the epidermis on the palms and soles; the nails are thick, there are crusts on the head, and the hair falls out. As this severe form is common in Norway, it is called Norwegian itch; and there is question as to whether it is due to the ordinary itch mite in neglected cases, to a distinct variety of the itch mite (*Sarcoptes scabiei var. Crustosæ*), or to the itch mite of the wolf.

When the patient bathes frequently, the lesions are always scarce.

Diagnosis.—The diagnosis is made on the basis of the symptoms: itching, especially severe at night, the lesions—burrows, papules, vesicles, blebs, pustules, and excoriations—and the distribution of the lesions. The parasites and their eggs may be found in a crust or in scrapings from the affected parts.

The presence of the lesions on the hands differentiates the condition from pediculosis.

Prophylaxis.—The underwear of the patient, as well as the bed-linen, should be *sterilized by heat*—preferably by boiling, or by dry heat if boiling would be apt to injure the clothing. If dry heat is used, great care is necessary that the garments shall be spread out, so that the heat will reach all parts of them. As the patient's outer garments are likely to contain some of the mites, they should be sterilized by exposure to dry heat, or by pressing with a hot iron. This sterilization of the clothing and bedding is important, not only to prevent the spread of the infection, but also to prevent reïnfection of the patient himself.

It is necessary to avoid close contact with an infected person, and not to sleep in a bed in which an infected person has slept, unless the bed-linen has been changed.

Treatment.—The treatment consists in the local application of substances which kill the mites, after thoroughly cleaning the skin, removing the crusts, and softening the epidermis so that the parasiticide can reach the mites.

The patient is given a **hot bath**, using plenty of soap—**green soap** if the skin is not too sensitive—and **rubbing the skin** with a coarse wash-cloth or with a soft brush. This removes the crusts, softens the epidermis, and opens up the burrows, so that the parasiticide can reach the mites.

Then an ointment is applied from head to foot, and well rubbed in, especially over the affected parts. **Sulphur, balsam of Peru, and beta-naphthol** are the drugs which are most used in the treatment of scabies; they may be used singly, or combined. Stelwagon advises an ointment of sublimed sulphur and balsam of Peru from 8 to 24 grams (2 to 6 drams) of each, and benzoinated lard and vaseline, 128 grams (4½ ounces) of each. For children and those with delicate skin, the milder strength is used. Beta-naphthol, 4 to 8 grams (1 to 2 drams), may be combined with the above mixture.

The ointment is rubbed in night and morning for from two to four days, the patient wearing the same underwear all the time. Ten or twelve hours after the last application, the patient takes a bath and changes his underwear, and his bed-linen is changed. The underwear and bed-linen are sterilized, to prevent reïnfection.

When the skin is sensitive, balsam of Peru may be used by itself, one application in full strength, and allowed to remain over night.

If the skin is very tough, or the condition is severe, as in Norwegian itch, Hardy's modification of **Helmerich's formula** (sublimed sulphur 2 parts, potassium carbonate 1 part, and lard 12 parts) may be used. This ointment is very irritating if the skin is at all tender.

Prognosis.—The condition, if untreated, tends to progress, and spontaneous recovery is said not to take place; hence, probably, the name "seven-year itch."

The condition clears up readily under treatment.

Pathology.—The female burrows in the epidermis, traveling in the stratum corneum, but not going as deep as the rete; the female lies at the end of the burrow, the eggs and feces being scattered along the burrow. The burrow is from 3 to 12 mm. (⅛ to ½ inch) long. Objectively the lesions are burrows, papules and vesicles, the burrows being the paths of the mites, and the papules and vesicles being the result of the venomous secretion of the mites. Scratching may give rise to secondary bacterial infection with the formation of pustules.

(c) *Acarodermatitis Urticarioides*

Synonyms.—Grain itch, straw disease, mattress disease.

Geographical Distribution and History.—In different parts of Europe a form of itch has been noted in persons who were employed in handling barley or wheat, or who lived in buildings where these cereals were stored, and it was found that this itch was due to a mite in the grain.

In different parts of the United States a form of itch has been noted in persons who slept on straw mattresses, or who used straw under the carpets. It also occurs in persons who handle straw, and in persons who handle grain. It has been noted in Massachusetts, Pennsylvania, Maryland, Ohio, and Indiana. Schamberg and Goldberger studied the condition in Philadelphia, where the disease was due to infected mattresses.

Etiology.—The disease is caused by *Pediculoides ventricosus* (Newport, 1850). The male is 120 microns (1/200 inch) long, and 80 microns (1/300 inch) broad. The non-gravid female is 200 microns (1/120 inch) long, and 70 microns (1/350 inch) broad. In the gravid female, the abdomen becomes an enormous sac (from 20 to 100 times the size of the rest of the mite) filled with embryos. The mouth-parts are formed for sucking, and the mandibles are needle-like.

Evolution.—The eggs hatch, and the young complete their entire cycle of development in the mother; so the young are born as sexually mature mites, which may wander about on the body of the mother, for a time, and soon copulate.

This mite is parasitic on the larva of soft-bodied insects. It has been found on wasp larvæ; but it lives especially on the larvæ of grain-destroying insects. As it destroys the larvæ on which it lives, *Pediculoides ventricosus* is of considerable importance in the preservation of grains; Herrera, in Mexico, has attempted to breed—without success—a Mexican species of the mite to destroy the larva of the cotton boll weevil.

But, especially in the United States, *Pediculoides ventricosus* lives mainly on the *wheat straw worm* (larva of *Isosoma grande*), the closely related *joint-worm* (larva of *Isosoma tritici*) and on the larva of the *Angoumois grain moth* (*Sitotroga cerealla*). Wherever these grain parasites are found, *Pediculoides ventricosus* is found.

The wheat straw worm is the common parasite of growing wheat west of the Mississippi river, and the joint-worm is the common parasite of wheat east of that river. The adults of Isosoma resemble minute or large black ants, with or without wings, with red eyes, and with legs more or less marked with yellow. The grain moth, introduced into North Carolina and Virginia from Angoumois, France, has spread through the Southern United States and as far north as Pennsylvania. The adult Sitotroga resembles a clothes moth.

Pathogenic Action.—It is probable that *Pediculoides ventricosus* must live as a parasite on animals. When grain is harvested, the mites will attack any animal; and when the grain is stored in barns, the mite readily attacks chickens, horses and cattle.

The mite readily attacks harvesters and any grain handlers, giving rise to "grain itch," "barley itch," "straw disease," and, since it readily attacks persons who sleep on new straw mattresses made from straw containing the mites, it is also known as "mattress disease." It attacks persons who do packing in straw. The mites on a sack of barley may appear as a red dust.

Schamberg suggested the name "grain itch" or "acarodermatitis urticarioides" for the condition caused in man by these mites, the former name to indicate that the mite may live in almost any cereal, the latter as a scientific descriptive name for the itch caused by this mite. The changes in the skin are those of urticaria.

Symptomatology.—When the mite gets on man, either from handling infected grain or straw, or from sleeping on new mattresses made from the infected straw (especially wheat), it at once plunges the rostrum into the skin, but it does not burrow. There is severe itching and burning, followed in a short time by the appearance of papules at the site of attachment of the mite. The commonest form of the eruption is a wheal with a central vesicle or pustule.

The eruption appears on the trunk, especially on the upper part, and on the neck and the upper part of the arms. It begins as erythematous spots, and in a short time a vesicle appears in the center, and changes to a pustule in a day or two. The vesicles may be so large as to resemble chicken-pox. The itching is intense, and scratching leads to the formation of crusts, and may lead to secondary bacterial infection.

The attack is accompanied by constitutional disturbances: chilliness, malaise, and nausea; and there may be fever up to 37.8° or 38.9° C. (100° to 102° F.). There may be albuminuria, and there is slight eosinophilia.

Diagnosis.—The history of the case is important. The distribution of the lesions is different from that of *scabies*. The vesicular lesions are different from *urticaria*. The small vesicles, sudden onset, and severe itching, and the frequency of the disease in adults, will differentiate the disease from *chicken-pox*.

Treatment.—The **source of the infection** must be **removed.** If it is a straw mattress, the mattress, bedding and clothing should be sterilized. In France, where the mites attacked workmen unloading a cargo of wheat, the wheat was washed and dried in the sun, and there was no more itch among the workmen.

As the mites do not burrow into the skin, but are on the surface and in the clothing, they are quite readily removed by frequent **warm baths with soap. Antipruritic applications** are required. Schamberg advises an ointment of **beta-naphthol,** 2 grams (30 grains), precipitated **sulphur,** 2.65 grams (40 grains), and **benzoinated lard,** 120 grams (4 ounces). This ointment not only kills the mites, but also relieves the cutaneous symptoms.

(*d*) *Other Forms of Acariasis*

Various sarcoptes on animals are varieties of *Sarcoptes scabiei. Sarcoptes scabiei var. equi* of horses, *Sarcoptes scabiei var. ovis* of sheep, *Sarcoptes scabiei var. capræ* of goats, *Sarcoptes scabiei var. cameli* of camels, *Sarcoptes scabiei var. suis* of hogs; *Sarcoptes scabiei var. canis* of dogs, and *Sarcoptes scabiei var. aucheniæ* of the llama, may be transmitted to man. Ordinarily the infection is short-lived, and the mite does not burrow in the skin; but at times the itch may be quite severe, and may persist for a couple of months.

The symptoms and treatment are the same as for sarcoptic scabies.

Tyroglyphus is a genus of free-living mites. They live in flour, sugar, cheese, and such food. They often attack insect collections. These mites produce "*grocer's itch*" when they get on the skin. When eaten with contaminated food, they may cause gastro-intestinal irritation, and the mites or their eggs may be found in the feces.

Tyroglyphus farinæ is the mite which causes "grocer's itch" in persons who handle flour and cereals.

A variety of *Tyroglyphus longior* produces itch in persons who handle copra.

Glyciphagus domesticus and *Glyciphagus prunorum* are two mites found in food. They may cause "grocer's itch," and may be found in the feces.

Tydeus molestus attacks persons who handle guano.

Trombidiidæ.—The Trombidiidæ (velvet mites, harvest mites) live free or on insects in the adult stage, and the larva is parasitic on vertebrates or other arthropods. The adults are red in color; they have tracheæ; the mandibles are hooked; the palps are free and armed. The legs are articulated on an epimerite.

The larvæ suck the blood or lymph of the host, and remain attached for a long time.

There are several genera, Microtrombidium (*Microtrombidium pusillum*) being an important mite in the United States. The adult commonly lives in bean and barley fields, in stubble, and on prairies or in the woods. It is about 2 mm. (1/12 inch) long, and is covered with branched hairs.

The larva is orange-red in color, and is abundant on grasshoppers, moles, and many of the small rodents. The paws of a mole may be red from the number of these larvæ on them. The larva frequently attacks man, and is the "red bug"; it is sometimes called "chigger" or "jigger." *Leptus autumnalis* is a name given to this larva.

PATHOGENIC ACTION.—In the summer and fall the larvæ get on man, and hold on by the powerful claws on their legs. The rostrum is plunged into the skin, and the tissues of the host form a tube around the rostrum. The irritating saliva causes the development of a papule with a purplish-red areola, which itches intensely (autumnal erythema).

Man is not a suitable host for the larva, and it dies in a few days on him.

TREATMENT.—Consists in rubbing the affected parts with **kerosene, lard,** or a piece of **bacon,** or applying **sulphur ointment.** Some men claim that by taking sulphur they are able to prevent the attacks of the mite.

Jackson says that in North Queensland, a species of leptus attacks persons in the scrub, giving rise to ceaseless irritation, which is known as "scrub itch"; and he says that this mite is an "irritating parasite that can give points to all ticks, sand-flies and mosquitoes in the world."

Trombidium tlalsahuate is a related mite which occurs in Mexico. The larva readily attacks man, selecting by preference the eyelids, the axilla or umbilicus, or the prepuce. It causes the same symptoms as does the "red bug."

There is a related mite, *Trombidium akamushi*, in Japan. The adult lives in woods and fields; the larva lives on the field mole.

The larva (*Kedani mite*) attacks man, and transmits Japanese river or flood fever (kedani). The bite becomes infected, and there is sloughing and ulceration, with lymphangitis. There is fever, the patient is profoundly intoxicated, and the condition is often fatal. It has been suggested that Japanese river fever is due to a specific virus, and that the field mouse is the reservoir for the virus.

(*a*) *Ixodiasis*

The *Ixodoidea* (*ticks, giant mites*) are of interest as the transmitters of *abesia* all over the world; they also transmit some of the blood spirochetes. In the ticks, hereditary transmission is common.

The Ixodoidea have tracheal stigmata in the posterior part of the body, at the base of the legs; the legs are articulated directly with the body; the mandibles are pseudo-hooked; the palps are free.

At the front of the body is a movable beak, *capitulum,* and the mouthparts together form the *rostrum.* The *hypostome* has teeth on the ventral surface; each mandible is in the form of a flattened shaft, and on the extremity of this shaft are articulated two pieces, armed with hooklets, which constitute a harpoon. These harpoons move laterally. The cuticle continues forward to form a sheath over the mandibles. The palps are large, and are frequently hollowed on the inner surface; they serve as protectors of the other parts of the rostrum.

The *adult* has four pairs of legs; the salivary glands are large, and extend nearly the entire length of the body. The male is smaller than the female.

EVOLUTION.—Taking *Ixodes* as the type: the female deposits her eggs under leaves. The *larva* (*seed-tick*) has three pairs of legs, no stigmata, and no genital opening. The larva climbs up on grass and shrubs, and fixes onto a host. It feeds, drops off, and molts to a nymph in a few weeks.

The *nymph* resembles the adult; it has four pairs of legs, and has stigmata, but has no genital opening. The nymph crawls up on grass and gets on another host, feeds, drops off, and molts to the adult tick.

The adults attach to another host, copulate, feed, and drop off. The male dies; the female deposits her eggs and dies.

There are two subfamilies: *Ixodinæ* and *Argantinæ.*

In Ixodinæ, the rostrum is terminal in all stages. In Argantinæ the rostrum is subterminal in the early larval stage, and is entirely on the ventral side in the adult.

The Ixodinæ are the "*hard ticks*" or "*wood-ticks.*" They have a dorsal shield (scutum) and the males of some species have chitinous plates on the ventral surface of the body. They may or may not have eyes in the margin of the scutum. The tarsi bear a pulvillus. There is a festoon on the posterior part of the body. The stigmata are large, and located behind the fourth pair of legs.

The female has a small scutum which covers only the front part of the body; the male has a scutum covering the whole dorsum. The larva and nymph have a small scutum.

The subfamily Ixodinæ is commonly divided into two groups: (1) *Ixodes* and *Amblyomma,* with the palps plainly longer than broad, and (2) *Rhipicephalus, Margaropus, Dermacentor* and *Hæmaphysalis,* with the palps no longer or only slightly longer than they are broad.

The Ixodinæ are mainly parasites of lower animals. Dermacentor readily attacks man.

The *Argantinæ* are the "*soft ticks.*" There is no scutum, no pulvilli, and the stigmata are behind the third pair of legs. The habits of these ticks are more like the habits of bedbugs: They feed generally at night and for a few hours at a time, except that the larva may remain attached for from five to eight days. The female does not die after depositing her eggs, but feeds again and deposits another batch of eggs. These ticks will live for a couple of years in a dish or pill box, without food.

There are two genera: *Argas* and *Ornithodorus.*

The species of *Argas* are nocturnal parasites of chickens, pigeons, and other birds; they occasionally attack mammals, including man.

The species of *Ornithodorus* frequently live in huts, and readily attack mammals and man.

Ticks may cause disease (*a*) as a result of irritation and infection of the wound made by the bite; (*b*) by the injection of some toxic substance—tick paralysis; and (*c*) by the transmission of pathogenic microorganisms.

(*a*) *Tick Bite*

Generally the bite of a tick causes only a slight irritation, which disappears in a few days; but persons vary in susceptibility, and in some persons the bite of even the common chicken-house tick (*Argas persicus*) leaves a papule which is covered with a crust and itches and exudes serum for several weeks. If, in removing a tick, the mouth parts are broken off and remain in the skin, there is apt to be infection, and there may be sloughing of the surrounding tissues.

The irritation from the bite of a tick varies greatly with different ticks, and Temple says that the bite of certain species of ticks causes severe local infection and sloughing, and that in Eastern Oregon it is not uncommon to see ulcers from infection of tick bites. Chandler says that the bite of a tick (probably *Dermacentor occidentalis*) caused an ulcerated area on his arm, and that the infection threatened loss of the arm if not of his life.

In Mexico and some parts of California, the *pajoroello tick* (*Ornithodorus coriaceæ*) is reputed to have a severe bite; and in some localities the natives fear the bite of this tick more than that of the rattlesnake. The bite is painful, and heals slowly, often with scar formation.

Herms studied this tick, and found that the bite produces hemorrhagic areas on lower animals.

In Mexico and the Southwestern United States, the *spinous ear tick* (*Ornithodorus megnini*) is common in the ears of lower animals, and it not infrequently gets into the external auditory canal of man. There is considerable pain while the tick is attached.

Treatment.—Removal of the tick is effected by applying to it some **bland oil** or **kerosene**, or **creolin**, thus stopping up the breathing stigmata; the tick loosens its hold and drops off in a minute or two. Or the tick may be removed by **excising** a small piece of skin at the site of attachment of the tick.

It is important not to remove the tick forcibly, as the mouth parts are broken off and remain in the skin, leading to local irritation with infection and sloughing of the tissues. When the mouth-parts of a tick have been broken off in the skin, they should be scraped out, tincture of **iodin** or other antiseptic applied, and the wound dressed.

When there is infection or sloughing, the wound is treated like a similar wound from any cause.

(*b*) *Tick Paralysis*

For a number of years a paralysis in sheep in Cape Colony and British Columbia has been associated with the bite of ticks: *Ixodes pilosis* in Cape Colony and *Dermacentor venustus* in British Columbia. In 1884, Bancroft reported that in Australia dogs and cats frequently die from muscular paralysis following tick bite; and he reported a case of tick bite in a woman, in which there were weakness and blindness.

In 1912, Temple reported 4 cases observed by himself, and 9 cases observed by other physicians, in Eastern Oregon, in which children suffered from acute paralysis of the ascending type, associated with the bite of a tick. At the same time Todd, in sending out letters to physicians, with a view to learning whether Rocky Mountain spotted fever existed in British Columbia, received reports of cases of paralysis in children, associated with the bite of a tick. In the same year, Cleland reported a case (communicated by Doctor Macdonald) of paralysis in a child in Australia, associated with the bite of a "bottle" tick (*Ixodes holocyclus*). Since that time additional cases have been reported from these regions, the represented area in the United States being extended to include Montana and Idaho.

Mechanism of the Process.—The mechanism of the condition is not clear. In man, the tick is usually found attached to the skin at the nape of the neck and in the hair about the occiput.

Hadwen found the ticks usually attached along the back-bone in sheep. He produced paralysis in lambs in three successive experiments by allowing from ten to twelve ticks (*Dermacentor venustus*) to attach themselves to the lamb. The paralysis occurred in from six to seven days after the ticks were put on the lambs. Hadwen and Nuttall produced paralysis in a dog by allowing one tick (*Dermacentor venustus*) to attach itself to the dog. Hadwen failed to produce paralysis in guinea pigs by allowing ticks to bite them, and Todd failed to produce paralysis in a guinea pig, pups, lambs, and monkeys, by allowing ticks (*Dermacentor venustus*) to bite them; he also failed to produce paralysis in mice, rats and a lamb by subcutaneous injections of extracts of ticks (Dermacentor and Margaropus).

Dermacentor venustus is a common tick in the regions in which tick paralysis occurs in the United States and British Columbia; but generally the tick has not been identified in the cases of paralysis.

Nuttall points out the frequency with which ticks are found on normal persons in the regions in which there is tick paralysis; and, while it is a definite affection, it does not appear to be due to any particular species of tick.

It is probable that the tick injects some toxin when it bites, but it is possible that the condition is due to a specific infectious agent which is injected by the tick. In experimental animals, the symptoms begin about six or seven days after the ticks attach themselves to the animal, and the onset of the symptoms corresponds with the complete engorgement of the tick. The experimental animals recover in from five to seven days.

Immunity.—Stuart says that one attack confers immunity; and Bancroft says that animals become tick-proof.

Symptomatology.—While most of the reported cases were in children, Todd received a report of a case in an adult.

In all of the cases the symptoms are practically the same, and, as pointed out by Temple, they are those of an acute ascending paralysis. The usual history is that the child was in its usual good health on going to bed at night, and that, on rising in the morning, it could not stand, and would fall in a heap on the floor on attempting to stand. There is no sensory disturbance; but there is motor paralysis, with loss of reflexes. As the condition progresses, the arms become involved, and if it is allowed to continue, the throat and tongue become involved and the child cannot swallow. The paralysis may progress to a fatal termination in young children.

In the beginning the temperature and pulse are normal; later the temperature may rise to from 38.8° to 40° C. (102° to 104° F.); the pulse becomes rapid, soft and weak; and respiration rapid. The paralysis progresses rapidly, being complete in from three to five days, and often causing death in that time. There were two deaths in Temple's cases.

On removal of the tick the symptoms at once disappear. There is marked improvement in from six to twelve hours, and the child is completely recovered in a day or two.

In Todd's investigation, he found that convulsions, stupidity and clumsiness were mentioned as due to tick bites; one physician wrote that it was the custom to look for ticks on a child with convulsions.

Treatment.—Removal of the tick is all the treatment that is required.

(c) *Transmission of Pathogenic Microörganisms*

Dermacentor venustus (Banks, 1897) transmits Rocky Mountain spotted fever. The infectious agent goes through a cycle of development in the tick (biological transmission), and the infection is transmitted through the egg to the next generation of ticks.

Ornithodorus moubata (Murray, 1884) transmits African tick fever, and the infection is transmitted to the next generation of ticks.

III. Order: Scorpionidea

Scorpions are abundant in the tropics, where some of them grow very large, and the sting of some of the larger scorpions is severe, and may be fatal. The last five segments of the abdomen are narrow, and form what is commonly called the tail of the scorpion. The two poison-glands are in the last segment, and open through a duct on either side of the curved spine which is used in stinging. The scorpion stings by swinging the tail forward over the dorsum, and striking in front of the head.

Scorpion venom is a clear fluid of an oily consistency, pale yellow in color, and faintly acid in reaction; it contains toxins which resemble those of cobra venom.

The symptoms resulting from the sting depend on the species, as well as the size, of the scorpion. In some of the small species, the sting causes only local pain, redness, and swelling similar to a bee-sting. In the large, tropical species, the pain is intense, and there are collapse and nervous symptoms. The pulse is weak and rapid, the respiration shallow, and there is profuse perspiration, nausea and vomiting. There may be convulsions, hallucinations, and mental depression. The patient may die in collapse, or the symptoms may abate in a few hours, and the general condition be normal the next day.

The sting is rarely fatal to adults; but it is not infrequently fatal to children. Wilson says that the sting of *Buthus quinquestriatus* is fatal to 60 per cent. of children under five years of age.

Treatment.—The sting of the smaller scorpions in an adult requires no treatment. The sting of the large tropical scorpions should be treated in the same way as snake bite, by the use of a **ligature, incision,** and **sucking out the venom.** The rubbing in of **potassium permanganate** crystals may be advisable; but it may cause sloughing of the tissues.

The *whip-scorpions* (*Vinegarone*) are not true scorpions, the last abdominal segments being very narrow, forming a whip-like tail. The giant whip-scorpion (grampus, mule-killer) is common in Florida and the southwestern part of the United States. The whip-scorpions have no poison-gland in the tail or the claws.

IV. Order: Araneida.

Spiders are found throughout the world; but the larger ones are found in the tropic and subtropical regions. The poison-glands are in the basal joints of the jaws, and open through a duct in the spine-like distal joint which penetrates the tissues when the spider bites. The venom of the spider resembles that of the scorpion in appearance and action, although the venom of certain genera of spiders seems to be much more toxic than the venom from other genera.

There is a great deal of popular misconception regarding the bite of spiders. The common spiders do not bite, or the bite amounts to no more than a pinprick when they do bite.

The *tarantism,* or *dancing mania,* of Italy during the Middle Ages, was supposed to be due to the bite of a spider, the European tarantula, *Lycosa tarantula.* It was really a form of hysteria.

The European tarantulas were *"wolf-spiders";* but the term has come to be applied to any large spider. The Russian tarantula is *Trochosa singoriensis,* and apparently the most formidable thing about it is its tiger-like striping. The tarantulas of the Western hemisphere belong to the *Avicularoidea.* The large spider commonly brought in with bananas is a giant crab-spider.

The spiders of the genus *Latrodectus* are small spiders; but they are generally considered to be venomous throughout the world, and wherever a spider enjoys a local reputation of venomousness it generally belongs to this genus. The "Karakurte" of Russia, the "Kapito" of New Zealand, the "Malmignatte" of Corsica and Southern Europe, and the "Mena-vodi" and the "Vancoho" of Madagascar, all belong to the genus Latrodectus. *Latrodectus mactans* is the black spider, with red and yellow markings—especially with red spots on the dorsum as found in the United States.

Experimental work has shown that the venom of Latrodectus is very toxic.

A few other spiders cause a severe bite. Some of the jumping spiders are known to have a severe bite. In the Philippines, a jumping arthropod is more feared by the natives than are the scorpions or centipedes; and it is possible that this is a jumping spider.

Apparently bacterial infection is rather common in spider bite, and a large part of the injury is due to this infection.

Symptoms and Treatment.—The local and general symptoms of a spider bite are the same as those of scorpion sting, and the treatment is the same. To lessen the danger of bacterial infection the wound should be opened and treated with **tincture of iodin** or some other antiseptic. If the bite becomes infected, it is treated like any infected wound.

The *Solpudiga* (*deer-killers*) are spider-like arthropods, with strong jaws. They have no poison-glands, but are capable of making severe wounds, with their jaws, and secondary bacterial infection seems to follow the bite quite frequently. The *treatment* consists in cleaning the wound to prevent bacterial infection.

C. CLASS: MYRIAPODA

In the Myriapoda, one order, the *Chilopoda*, or *centipedes*, are venomous. The poison-glands are in the basal joint of the first pair of legs, which are bent forward and modified so as to be used in holding their prey. The poison-glands open through a duct at the tip of the powerful, spine-like claw which terminates this pair of legs. The venom is like that of the scorpion.

The local and general symptoms resulting from centipede bite are practically the same as those from scorpion sting, with a tendency to more local reaction.

The bite shows two punctures. As the legs have no poison-glands, it is difficult to account for the frequently reported cases in which the centipede, in traveling over the skin, has left an urticarial trail. It is possible that some of these cases have been cases of caterpillar sting.

The *treatment* generally does not need to be as energetic as that for scorpion sting or spider bite; it usually suffices to bathe the bitten area with **ammonia. Cold or hot applications** may be necessary to reduce the local inflammation; and **morphin** may be necessary to relieve local pain.

Centipedes may get into the nasal fossæ or into the gastro-intestinal tract, and may live there for some time; but they cannot multiply there. Their presence in the intestinal tract gives rise to much the same symptoms as do various worms; but vermifuges do not remove them.

D. CLASS: INSECTA

In the insects, there are three distinct parts to the body: head, thorax, and abdomen. The *head* bears the eyes, antennæ, and mouth parts.

The *mouth-parts* consist of:

1. Labrum or epipharynx, which may be compared to the upper lip.
2. Hypopharynx, which may be compared to the tongue.
3. Two maxillæ, each with a maxillary palp.
4. Two mandibles.
5. The labium, which may be compared to the lower lip, with labial palps. The labium commonly acts as a sheath for the other mouth parts.

The *thorax* bears three pairs of legs, and one or two pairs of wings. The wings may disappear in parasitic forms.

The *abdomen* is segmented, and is terminated by a genital armature in both sexes.

Insects may go through a complete or incomplete metamorphosis.

Complete Metamorphosis.—The egg gives rise to a larva which does not resemble the adult; the larva molts to form a nymph; and the nymph molts to form the adult insect—as in the butterfly and mosquito.

Incomplete Metamorphosis.—The larva resembles the adult, differing only in size, absence of wings, and absence of external genitalia. The larva molts to form the nymph, which molts to form the adult—as in bugs.

I. *Order: Hemiptera*

This order includes the bugs. The anterior part of the wing may be chitinous; the posterior part membranous.

(1) *Suborder: Aptera*

The Aptera have no wings, as they are all parasites and have lost their wings.

Of the Aptera, the *Pediculidæ* are important parasites of man. The pediculidæ have a long head and small, sucking mouth-parts.

In the genus *Pediculus* the thorax is narrower than the abdomen, and is plainly separated from the abdomen. There is a neck between the head and the thorax. The stigmata are in the third to eighth abdominal segments.

The genus *Phthirius* is characterized by a broad thorax, with no separation between the thorax and abdomen.

Until recently it has been considered that there were two species of pediculus: *Pediculus capitis* or the head louse, and *Pediculus corporis* or the body louse. But Nuttall, Bacot and others have shown that the head louse and the body louse are merely varieties of the same louse, and the name should be *Pediculus humanus var. capitis* for the head louse, and *Pediculus humanus var. corporis* for the body louse. Bacot showed that the two varieties cross readily, and that the offspring are fertile.

Phthirius pubis is the pubic louse, or crab-louse.

Pediculus humanus and *Phthirius pubis* are discussed in the section on Typhus Fever (Volume IV, pages 429 ff.).

Infestation with lice is known as:

(*a*) *Pediculosis*

Synonyms.—Phthiriasis, vagabond's disease.

The three lice of man are so strictly adapted that it is only rarely that they invade each other's sphere of action.

When the louse bites it inserts the suctorial tube deep into the skin, and injects the irritating saliva. When the suctorial tube is withdrawn, the blood fills the wound in the skin, forming the tiny drop of blood which appears in the skin at the site of the bite. The irritating saliva causes itching, and scratching leads to excoriation. There may be an eczematous condition; and when the skin lesions become infected with bacteria, pustules are formed. When the condition is prolonged, the skin becomes thickened and pigmented—"vagabond's disease." This pigmentation is probably due, in part at least, to some substance in the saliva of the louse.

The saliva of *Phthirius pubis* contains a special toxin which causes steel-gray spots on the skin—*maculæ cæruleæ,* or Morrison's spots. These spots can be produced by the injection of crushed *Phthirius pubis;* but it seems that a predisposition in the person is necessary. These spots are said to be pathognomonic of the pubic louse.

Symptomatology.—The symptoms of the three varieties of pediculosis are much the same; but there are certain peculiarities of each variety.

PEDICULOSIS CAPITIS.—The symptoms vary from slight itching of the scalp, especially below the occiput and near the margin of the hair at the back of the neck, to intense itching, with the formation of papules, excoriations, pustules and crusts. There may be an eczematous condition of the skin; and in neglected cases the hair may be matted together by the crusts.

PEDICULOSIS CORPORIS.—There is itching, which may be generalized. The red point of blood, at the site of the bite in the skin, is frequently seen; and there are excoriations from scratching. As the lice live in the clothing, and only come onto the body to feed, the lesions are found in the regions where the clothing comes in closest contact with the body, especially across the shoulders and about the neck, around the waist, over the sacrum and down the outside of the thighs. In prolonged cases there may be pigmentation of the skin.

PEDICULOSIS PUBIS.—There is itching, with the formation of papules, pustules and excoriations. The lesions are generally limited to the pubic region, but they may extend to the lower part of the abdomen.

The crab-louse may get on other parts of the body than the pubes, as the hairy part of the breast, axilla, legs, beard, eyebrows and eyelashes. They produce the same lesions in these regions as in the pubic region.

Diagnosis.—The diagnosis of pediculosis capitis is made by finding lice in the hair, and eggs (nits) attached to the hair. A pustular eruption at the back of the head leads to suspicion of pediculosis.

The diagnosis of pediculosis corporis is made by finding the lesions on the body, especially hemorrhagic points, excoriations, parallel scratch marks, and pigmentation, and by the distribution of the lesions. The distribution—especially the freedom of the hands—is of value in differentiating *scabies* from pediculosis. It is often necessary to search very carefully in the seams of the underclothing to find the lice. The eggs are found along the seams in the underclothing, and they may be found on the body hairs, especially the fine, down hairs.

The diagnosis of pediculosis pubis is made from the lesions and their distribution, and on finding the lice clinging to the hairs, close to the skin, and the eggs attached to the hairs.

Treatment.—The methods for the destruction of lice are discussed in the section on Typhus Fever (Volume IV, pages 434 ff.).

The skin lesions promptly disappear on removal of the lice. If the skin irritation is severe, it may be treated with a saturated solution of **boric acid** with 1 per cent. of **carbolic acid**, or with **zinc ointment** with 1 per cent. of carbolic acid.

In addition to *typhus fever, Pediculus humanus var. corporis* transmits *trench fever*. The English Commission showed that trench fever was transmitted by rubbing the dried feces of infected lice, or the crushed lice, into an abrasion of the skin; biting experiments failed. The American Red Cross Commission showed that trench fever was transmitted by the bite of infected lice.

Relapsing fever is transmitted by crushing an infected louse on the skin; but biting experiments have failed to transmit the infection.

Phthirius pubis does not transmit any disease.

(2) *Suborder: Heteroptera*

The heteroptera have two pairs of wings, the first pair with the anterior half chitinous, the second pair membranous; that is, the first pair of wings is hardened at the base to form wing covers. The beak is moderately turned back under the body. They have a gland which secretes a substance with a strong odor: in the adult, the opening of this gland is on the ventral surface of the thorax, at the level of the third pair of legs, the opening being readily seen with the naked eye in large specimens.

Many of these insects bite man, some of them accidentally, in defending themselves, others for the purpose of sucking blood. Two families, *Cimicidæ* or bedbugs, and *Reduviidæ* or "assassin-bugs," contain parasites of man.

Cimicidæ.—In the cimicidæ, the head is broad and short, with two large black eyes; the antennæ have four segments; the beak is grooved and has three segments; the body is flat; the hind wings are absent. The biting mouth-parts lie in the groove in the three-segmented beak or *labium*. The maxillæ and mandibles are long bristles, barked at the ends. The mandibles have a "double-barreled" groove on the apposed surfaces; the saliva is injected down one groove, and the juice or blood is drawn up the other groove. The maxillæ support the mandibles.

Cimex lectularius is the common bedbug throughout the world. The adult is from 4 to 5 mm. (1/6 to 1/5 inch) long and 3 mm. (1/8 inch) broad.

The female deposits several batches of about fifty eggs during her life. The pearly-white eggs are deposited along the seams of the mattresses, in cracks in beds and other furniture, in cracks in the wall, and under loose wall-paper. The egg hatches in from eight to ten days, the larva being yellowish-white, and resembling the adult except that it has no wings and no genital opening. The larva molts five times, and becomes the adult bug in from six to eleven weeks.

Besides living in beds, the bedbug lives in other furniture, as wicker chairs, in cracks in the walls, and even in cracks in the floor. In appears that living in beds is a comparatively recent habit of the bug, and that they formerly lived almost exclusively in the walls—hence the name, *wall-louse*. The larvæ may be found on books, especially about the part where the binding is glued on; they are not to be confused with book-lice—the Psocidæ.

Bedbugs can travel from house to house; but they are more commonly carried on clothing, or in furniture and bedding.

It is commonly stated that bedbugs live in lumber and in the woods, where they may be found in cracks in and under the bark of trees; but Riley and Johannsen point out that these bugs are entirely different from the bedbugs.

It is also stated that bedbugs live in poultry houses, and are found on bats and in the nests of swallows. While *Cimex lectularius* may infest chicken houses, the common cimex found about poultry-houses and dove-cots is *Cimex columbarius*, and the bugs of bats and swallows are different from the common bedbug.

PATHOGENIC ACTION.—The biting takes about ten minutes, and then the bug quickly withdraws the biting parts and hurries away to hide. The susceptibility of persons to the irritating saliva varies; in some persons it causes no inconvenience; in others, the bite begins to itch a couple of minutes after the bug begins to bite, and there may be a small wheal surrounded by a zone of erythema.

The disagreeable odor is due to the secretion of the thoracic gland found in this suborder.

The bedbug is not known to transmit any pathogenic microörganisms; but it is possible that it transmits European relapsing fever. The spirochete of relapsing fever will live five days in the intestinal tract of the bedbug; but all attempts to transmit the infection by the bite of the bug have failed.

The bedbug can transmit plague for four days after biting a plague patient.

The Indian bedbug, *Cimex hemipterus,* is widely distributed in tropical and subtropical regions, and has the same habits as *Cimex lectularius*. Brumpt has shown that it can transmit *Trypanosoma cruzi* in the feces. Patton suggested that it transmits oriental boil, and Rogers has suggested that it transmits kala azar. It can transmit the spirochete of Asiatic relapsing fever.

PROPHYLAXIS.—Cockroaches and ants are enemies of the bedbug.

Iron bedsteads are most easily kept clean, and all mattresses and bedding should be kept clean.

When it is desired to disinfect only a bedstead or some article of furniture, a liberal application of **kerosene** is the best. Various substances, such as oil of wintergreen, may be added to overcome the disagreeable odor of the kerosene. A number of preparations of **naphtha** or **gasoline**, which do not stain walls, are sold in the market.

Castellani and Chalmers recommended **acetic acid** for application to the infected areas.

As the bugs are commonly in the walls and furniture, fumigation is the most satisfactory method of destroying them. **Sulphur fumigation** in the ordinary way, using 2 pounds of sulphur for every 1,000 cubic feet of space, is used.

Reduviidæ.—The Reduviidæ are an interesting family of insects. Most of them live free; some of them will bite in defending themselves; and there are all stages of parasitism, up to some that have become strictly parasitic. Some of them are robber parasites of other bugs; and some of them seem to have become to some extent parasitic on man in this way. Thus, some of the conorhinids (cone-nose bugs) are supposed to have acquired a taste for human blood through their habit of catching bedbugs and sucking the body-juices out of them. Then the conorhinids found that they could obtain their blood by going direct to the source, rather than by taking it second-hand from the bedbugs. Darwin, in his "Voyage of the Beagle," speaks of the attack (saying it deserves no less a name) of the Benchucha, the great black bug of the pampas, and describes how fearlessly the bug would feed on the finger of a man. The bite of some of these bugs causes severe pain, while the bite of others causes little or no pain.

These bugs will live for months, or even years, without food.

In the genus *Triatoma,* the head is long, conical or cylindrical; the pre-ocular part is longer than the post-ocular part; the antennæ are twice as long as the head, and are inserted midway between the eyes and the tip of the snout; the first segment of the beak is much shorter than the second segment; the wings are well developed.

Triatoma sanguisuga, one of the *"big bedbugs,"* the *"Texas bedbug,"* the "blood-sucking cone-nose," is widespread in the United States, and is at least one of the bugs known as "kissing-bugs," although a related bug, *Reduvius personatus* ("masked bedbug hunter"), is probably the more common "kissing-bug." *Triatoma mexicana* is common in Mexico, and is the *"Mexican bedbug."* *Triatoma indictiva* is common in Arizona and Texas, and is closely related to *Triatoma sanguisuga.* *Triatoma infestans* is Darwin's *"great black bug of the pampas."* *Triatoma rubrofasciata* is common in India, and Donovan has suggested that it is the transmitter of kala azar.

Triatoma megista is common in the state of Minas Geraes, in Brazil, where, from its habit of biting about the face, it is known as *"barbiero"* (the barber). The bug lives in the houses, and sucks blood from the sleeping inhabitants at night, very much as does the common bedbug. The bite is not painful.

This bug is the transmitter of *Trypanosoma cruzi* in Brazil. Its connection with trypanosomiasis is discussed in Volume IV, page 259.

Rhodnius prolixus is common in Venezuela, where it lives in the houses, very much as does *Triatoma megista* in Brazil.

This bug is the transmitter of *Trypanosoma cruzi* in Venezuela. Its connection with trypanosomiasis is discussed in Volume IV, page 259.

II. Order: Hymenoptera

This order includes the bees, wasps, hornets, and ants.

Apidæ.—The Apidæ include *Apis mellifica,* the *honey-bee; Bombus hortorum,* the *bumble-bee; Vespa vulgaris,* the *wasp; Vespa crabo* and *Vespa orientalis, hornets.*

There are two, and sometimes three, poison-glands in the abdomen; these glands open into the sheath about the sting. The sting consists of a central shaft and a pair of barbed darts. The venom contains formic acid; but this is not the active principle of the venom. The venom resembles cobra venom, containing substances which produce local inflammation, substances which affect the nervous system, and substances which produce hemolysis.

Persons who work with bees, and are stung frequently, acquire an immunity to the venom; but this immunity frequently does not last from one year to the next.

Symptomatology.—The symptoms resulting from the sting are generally nothing more than local pain, redness, and swelling. But persons vary greatly in susceptibility, and some persons are nauseated and may have quite marked constitutional disturbances due to the sting. In the case of multiple stings, or in sting from some of the hornets, there may be considerable constitutional disturbance, amounting even to collapse. Later, there may be slight fever, with edemas, urticaria, or a macular eruption on different parts of the body.

Treatment.—In the case of the honey-bee, the sting, with the poison-glands attached, is frequently left in the wound; but, in the case of the other bees, wasps, and hornets, the sting is not left in the wound. When the sting is left in the wound, it should be removed by lifting out with a knife, so as to avoid squeezing any more venom into the wound. **Hot applications** are of the greatest value. **Alkalis,** as soda or dilute ammonia, are commonly applied with the idea of neutralizing the formic acid; but as formic acid is not the important toxic substance in the vemon, these alkaline applications do little good.

Formicidæ.—The formicidæ, or ants, have the poison-glands at the base of the jaws, and the venom is injected by biting. Ordinarily the bite of an ant amounts to no more than a sharp stinging, with possibly the development of a wheal at the site of the bite. But, in the tropics, the bite of some of the large ants is very painful, and may cause faintness, and at times temporary paralysis.

The venom contains formic acid; but, from the severe effects of the bite of some of the tropical species, it appears that the venom must contain other toxic substances as well.

In Ceylon, a small ant gets into the beds and bites the sleeping people.

TREATMENT.—Treatment consists in **bathing** the affected part with a dilute **solution of ammonia.**

Ants may be kept out of beds by placing the legs of the bed in cans filled with water (with a layer of oil on top, to prevent mosquito-breeding), or by sprinkling *powdered camphor* between the sheets.

III. Order: Coleoptera

This order includes the beetles and weevils.

The larvæ of beetles may be accidental parasites of man, especially in the digestive tract. Usually it is the larva of the weevils, but there are cases in which other beetle larvæ, and even adult beetles, have been passed in the feces. The larvæ are probably taken in with the food. Infestation with coleopterus larvæ is known as *scoleciasis.*

One case is reported in which the larva of a beetle of the genus *Necrobia* was found in a tumor of the conjunctiva. This larva normally lives in decomposing flesh.

The body fluids of some of the beetles and their larvæ contain toxic substances. Thus body-fluid of the larva of the chrysomelid beetle is used as an arrow poison by some of the South African natives.

The blister-beetles, of which the "Spanish fly" is an example, have a vesicating substance in the body fluid.

The larvæ of some beetles act as the intermediate host of *Gigantorhynchus gigas.*

IV. Order: Lepidoptera

This order includes moths and butterflies.

The larvæ of the common cabbage butterfly may be taken into the intestinal tract in eating raw cabbage. Ordinarily it causes vomiting, and the larvæ are brought up in the vomitus.

The hairs of caterpillars may lodge in the conjunctiva or cornea, and give rise to nodular conjunctivitis. The condition resembles tuberculous nodules on the conjunctiva; but one or more caterpillar hairs are found in the center of each nodule.

The larvæ of some moths and butterflies have fine hairs over the body, these hairs being connected with secreting cells in the skin; the secretion is poisonous, and produces a nettling effect.

The most important of these nettling larvæ is the caterpillar of the *brown-tail moth* (Euproctis crysorrhœa). This moth seems to have been brought into the United States from Holland with roses, and has spread over New England and Canada. It is destructive to fruit trees. It lives especially on corn and on the willow.

A number of cases of *brown-tail moth dermatitis* have been reported. The caterpillars have in addition to the ordinary hairs on the body, tufts of minute barbed hairs in rows on the body; these hairs are on tubercles, and the epithelium underlying these tubercles contains large secreting cells which are connected with these hairs. These hairs are less numerous on the cocoon and the moth. They penetrate the epidermis and the corium, and contain an irritating substance which causes exudation of fluid into the epidermis, and necrosis of the epidermis.

The dermatitis is most frequently seen about the end of May and in June, when the caterpillar has completed its growth. The first symptoms are itching, with the appearance of macules or wheals. The eruption occurs most commonly on the face, neck, arms, and upper part of the body. The itching is intense, and, in extensive lesions, there may be constitutional disturbances. The eruption lasts from a few days to several weeks.

Treatment.—Treatment consists in the use of soothing **alkaline solutions**, and **antipruritics**, as carbolized solutions and ointments.

Other caterpillars having nettling hairs are the *flannel-moth;* the *saddle-back caterpillar*, and the *Io moth.*

The caterpillars of various butterflies cause skin eruptions in the tropics.

There is a great amount of popular misunderstanding of the caterpillars which may cause irritation of the skin. The various caterpillars with large spines and horns are popularly feared; but it is generally the smaller, hairy caterpillars which possess the nettling hairs. Thus, the "tomato worm" and the caterpillar of the "regal moth" do not have any nettling hair or poisonous action.

V. Order: Orthoptera

This order includes the cockroaches. Stiles reports the finding of a mass of cockroaches in an abscess of the jaw.

The cockroach has been accused of transmitting various bacteria, as paratyphoid bacilli; but nothing definite is known on this subject.

VI. Order: Diptera

The diptera have two pairs of wings, the posterior pair being atrophied and transformed into balancers. The proboscis serves for sucking, and is more or less modified and adapted to the mode of life of the insect.

Metamorphosis is complete. The larva has no legs, and may or may not have a head. After varying periods of time in the larval stage, the insect enters the nymph stage (during which it does not feed), and from this the adult emerges.

The eyes are compound; the antennæ rise between the eyes.

(1) Suborder: Aphaniptera

The Aphaniptera include the fleas. They are laterally compressed insects, with the mouth-parts formed for piercing and sucking. All of them are strictly parasitic, and all have lost their wings. The head is broadly articulated with the thorax; all three segments of the thorax are distinct, and the abdomen is distinctly segmented.

Two families: *Pulicidæ* and *Sarcopsyllidæ*, contain parasites of man.

Pulicidæ.—The pulicidæ are ectoparasites, rarely limited to one host. They feed frequently, and during feeding, they expel fluid from the anus, and also regurgitate the contents of the stomach into the wound made in biting.

In the adult, the head is large and irregularly conical. There may or may not be eyes. There may be combs on the cheek or lower edge of the head. The antennæ consist of two basal segments and a large oval segment or club; there are nine rings on the club. In repose the antennæ lie in definite grooves above and behind the eyes.

MOUTH-PARTS.—The maxillæ are dependent, triangular flaps; and their stout palps project like antennæ from the lower part of the head. The labial palps lie between the maxillæ, and form a sheath for the piercing parts. The mandibles are needle-like, serrated, and longitudinally grooved; by their apposition they form a tube for the passage of the saliva. The hypopharynx is short. The epipharynx is an unpaired bristle, grooved ventrally, which, by apposition with the mandibles, forms a tube through which the blood is sucked up.

The *thorax* bears three pairs of legs. The *abdomen* is segmented. There are two pairs of large salivary glands in the thorax. The pharynx is large and muscular, and acts as a pump.

EVOLUTION.—The eggs are passed in the hairs or clothing of the host, and fall on the floor, or in the bedding or nests of animals. In from one to several days a vermiform larva hatches out. The larva feeds on débris, especially on the feces of the adult flea. The larva molts, and in a few days retires to a secluded place, folds on itself and forms a cocoon about itself. In a few days it changes to a hump-backed nymph, which has a faint resemblance to the adult insect. After a time, the adult emerges from the cocoon. The entire cycle, from egg to adult, takes about a month.

VARIETIES OF PULICIDÆ.—*Pulex irritans* is the human flea, although it will bite many animals. The eggs are deposited anywhere, and they collect in the dust and dirt in the cracks of the floor. The evolution is as described.

In some parts of the world this flea is abundant in the houses; it causes great annoyance by its bite and by crawling over the body. In some parts of South America, we preferred to set up our beds and sleep in the open, to avoid the annoyance of the fleas. Darwin speaks of the same thing, and says that there was not a space on his legs the size of a shilling which had not its red mark where the flea had feasted.

Ctenocephalus felis and *Ctenocephalus canis* are the cat and dog flea; and they readily bite man. They are also found on rats. These are the common fleas in the houses in the eastern part of the United States, where cats and dogs are kept in the houses.

The eggs are deposited in the hair of the cat and dog, and fall off onto the floor. Verrill collected a teaspoonful of eggs from a woman's dress, after she had held a kitten in her lap for a short time; and Patton and Cragg say that the inside of a hat in which a kitten had slept was so covered with eggs that it looked as though it had been sprinkled with sugar.

Xenopsylla cheopis is the rat flea of the tropics; it readily bites man and other animals, especially when rats are not available.

Ceratophyllus fasciatus is a common rat flea.

Ctenopsylla musculi is a common flea of rats and mice.

PATHOGENIC ACTION.—The bite of a flea causes a wheal which itches for a varying length of time. Persons vary greatly in their susceptibility to the venom of the flea. In some persons the bite causes nothing more than a wheal that disappears in a short time, with little or no itching. In other persons, the bite causes a papule which itches at intervals for days.

Pulex irritans can transmit plague experimentally, but it plays no part in the transmission of plague in nature.

Ctenocephalus felis and *Ctenocephalus canis* can transmit plague experimentally; but they are not good hosts for the plague bacillus, and the experiment often fails. They play no part in the transmission of plague in nature. They are the intermediate host of *Dipylidium caninum.*

Xenopsylla cheopis is the transmitter of plague in nature.

Ceratophyllus fasciatus and *Ctenopsylla musculi* play no part in the transmission of plague in nature. The cysticercus of *Hymenolepis nana* and of *Hymenolepis diminuta* has been found in the body cavity of *Ceratophyllus fasciatus.*

PROPHYLAXIS.—The larvæ of *Pulex irritans, Ctenocephalus felis* and *Ctenocephalus canis* live in the dust in the cracks in the floor, and in the carpets and rugs on the floor. The **floors** should be kept well **swept,** so that there is no accumulation of dust in the cracks. As the larva is delicate, and does not stand light well, it is readily destroyed. The floors may be **scrubbed with soap and water,** or may be oiled with **kerosene** or some of the preparations on the market. Rugs are preferable to matting or carpets on the floor, and the rugs should be taken out and cleaned frequently.

A flea-infested room may be fumigated with **sulphur**—2 pounds to each 1,000 cubic feet of room space. Fumigation with **hydrocyanic acid gas** *is effective,* but it must be used with great care, as it is very poisonous. A satisfactory method of ridding a house of fleas is to sprinkle flake **naphthalin**—about five pounds for an ordinary-sized room —over the floor, and close the room for twenty-four hours. The naphthalin may then be swept up and used for another room. Naphthalin kills the adult fleas and the larvæ, but does not kill the eggs; therefore the treatment must be repeated in two weeks, or the floor must be scrubbed with soap and hot water. Chandler suggests the use of **sodium fluorid,** blown over the floor with a dust-gun. Many adult fleas may be collected in a room by having a person, with sticky fly-paper around his legs and ankles, walk about in the room.

If it is desired to keep cats and dogs in the house, they should be given a rug to sleep on, and should be given frequent baths with some of the **flea soaps**. The rug on which they sleep should be shaken and beaten frequently, and the dust burned.

When one has to sleep in an infested house, a great deal of relief is obtained by sprinkling insect-powder freely between the sheets; and, in flea-infested regions, it is advisable to carry a supply of insect powder for this purpose.

Sarcopsyllidæ.—The Sarcopsyllidæ are the penetrating fleas.

Dermatophilus penetrans is the *chigger* or *chigoe*. It occurs in Central and South America and in the West Indies. It appears to have been introduced into West Africa with sand from Brazil. It spread across the tropical zone of Africa, and reached Madagascar. It has been repeatedly introduced into India, by infected persons from Africa, but it has never gained a foothold there. The males and non-fertilized females live in houses, stables, or in the fields, and live in the same manner as the ordinary fleas. They attack man, as well as domesticated and wild animals; and in West Africa it is noted that they especially attack pigs.

The fertilized females plunge the mouth-parts into the skin, and gradually work their way into the epidermis—especially the thick, soft epidermis about the toe-nails—and feed on blood in the papillary zone of the skin. In some days the abdomen becomes a sac filled with eggs, and the head and thorax of the flea amount to no more than an appendage on the side of the sac-like abdomen.

When the eggs in the flea have reached maturity, they are passed, and the female dies. The development of the larva and nymph is the same as in the ordinary fleas.

PATHOGENIC RÔLE.—When the female is working her way into the epidermis, there may be no itching; usually, however, there is quite marked itching, more severe at night. The flea works her way into the epidermis until only the last abdominal segment protrudes from the opening. As the flea enlarges, there is pain and inflammation at the site of penetration; and there may be ulceration. If the flea is not disturbed, she passes the eggs out through the opening in the epidermis, and then dies; or, as Brumpt says, she leaves the skin in a few days, and falls to the ground to deposit her eggs, passing the eggs while in the skin only when an abscess forms and the flea dies. If attempts are made to remove the flea, after she is embedded in the skin, and she is ruptured, there is considerable inflammatory reaction, and sometimes sloughing of the tissues.

Chiggers are numerous in the feet of natives, especially those with sleeping sickness or some other condition in which they are not able to take care to remove the fleas before they have worked their way into the epidermis.

Brumpt considers that tetanus is more common in malarial persons in the regions in which chiggers are abundant. He holds that the chigger introduces the tetanus bacillus into the skin, and that the subcutaneous injection of quinin for malaria favors the development of the tetanus bacillus.

SYMPTOMATOLOGY.—The symptoms are itching, and the frequent development of inflammation and suppuration about the embedded parasite.

TREATMENT.—*Prophylactic.*—Prophylaxis consists in keeping the **floors** of the house **clean,** and in keeping lower animals away from the house. Jeanselme and Rist recommend daily washing of the feet, and never going bare-foot, even in the house. Castellani and Chalmers recommend wearing **boots,** and inspection of the feet every morning, for fleas; if any are found they should be **removed with a knife.**

Curative.—*Treatment* consists in **removal of the parasite.** The flea is readily removed in the first day or two after she has penetrated the epidermis. Jeanselme and Rist say that the native women and children are very adept at removing the flea; they pass a needle into the opening in the epidermis and, by sweeping it around, remove the flea. **Tincture of iodin** or other antiseptics, and an aseptic dressing, should be applied to the wound. When there is suppuration, it should be treated as any suppurating wound.

Echidnophaga gallinacea is the *chicken-flea,* or *sticktight flea,* of tropical and subtropical regions. While it is commonly found on chickens and other poultry, it also attacks domestic animals and man. The fleas collect in masses about the head of chickens, and in the ears of other animals; and, as it burrows slightly in the epidermis, it maintains its hold very firmly.

The following table, arranged by Dunn, serves for the identification of the more common fleas:

1. Head pointed in front; abdomen round and distended, *Dermatophilis penetrans*
   Head angulated in front; thoracic segments narrow, *Echidnophaga gallinacea*
   Head rounded in front; thoracic segments wider.........2
2. Comb of spines present on edge of head or prothorax......3
   No such comb present....................................6
3. Comb on both head and prothorax.........................4
   Comb on prothorax only...........*Ceratophyllus fasciatus*
4. Comb on head small; no eye present.....*Ctenopsylla musculi*
   Comb on head heavy and of same size as on prothorax; eye present...5
5. Head rounded in front................*Ctenocephalus canis*
   Head elongated and not so round.........*Ctenocephalus felis*
6. Eye pointed below; bristle arising from in front of and opposite its lower border; spermatheca knob shaped at one end, not crescent form....................*Pulex irritans*
   Eye round; bristle arising from in front of and opposite its upper border; spermatheca nearly uniform throughout, and almost crescentic in form.......*Xenopsylla cheopis*

(2) *Suborder: Brachycera*

The suborder Brachycera includes all of the organisms which we know as *flies*. The antennæ are short, and composed of three segments; the last segment, often large, is provided with an antennal bristle or arista, simple or jointed, naked or hairy. The body is plump; the wings are large and the wing venation is complex.

Tabanidæ.—The family Tabanidæ are the *gadflies, horse-flies,* or *deer-flies.* The head is large, in the male, composed almost entirely of the eyes. There is a shiny streak between the eyes in the female. The antennæ consist of three segments, the third segment consisting of from four to eight subsegments, incompletely fused.

The mouth-parts are formed for stabbing and cutting. The labium is large and fleshy, and the labellæ are large. The epipharynx is dagger-shaped, and is ventrally grooved. The hypopharynx is dagger-shaped, with a canal through it. The mandibles are lancet-shaped, and atrophied in the male. The maxillæ are distally serrated. The maxillary palps are stiffly pendent, and consist of two segments, of which the second is often large and tumid.

In biting, the maxillæ and mandibles cut an opening in the skin, and the epipharynx and hypopharynx are pushed into the wound. The saliva is injected down the canal in the hypopharynx, and the blood is drawn up through the tube formed by the apposition of the epipharynx and the hypopharynx.

The adult flies live in the woods and pastures, the males living on plant juices, the females being active blood-suckers. They are not apt to come into the house, and do not bite man very much.

The eggs are deposited in masses on leaves and stems of plants growing in marshy ground or overhanging the water. The larvæ live in wet earth, decaying vegetation, or in water, and are carnivorous. The pupa resembles a butterfly pupa, and lives in moist earth or water. The complete development, from egg to egg, takes about eleven months.

The Tabanidæ are a large family, about 2,500 species being known. They are found throughout the world, even at an altitude of 15,000 feet.

Four genera: *Tabanus, Hæmatopota, Pangonia,* and *Chrysops,* are important.

Chrysops (deer-flies) transmit *loa loa* in Africa.

Syrphidæ.—The family Syrphidæ are the *hover flies* or *drone flies.* They are bee-like flies, although some of them resemble the *blue-bottle* and *green-bottle* flies. The adults hover over or settle on flowers, and feed on pollen and the juices of flowers; the larvæ are carnivorous, and destroy various insects, which are parasitic on plants. The larva has a long breathing tube; hence its name, *rat-tail larva. Eristalis tenax* is one of the common drone flies, and the *rat-tail* larva of this fly is one of the most common larvæ found in intestinal myiasis.

Sepsidæ.—The family Sepsidæ are small, usually black, flies, with a constricted waist. The eggs are deposited in decaying vegetable and animal matter. The larvæ are frequently found in cheese and bacon; and, from their ability to jump or skip, they are known as *cheese-skippers. Piophila casei* is the common cheese-skipper fly. As cheese containing skippers is esteemed by some people, these larvæ are not uncommonly found in intestinal myiasis.

Muscidæ.—The family Muscidæ is a large family. There are four subfamilies, one of which, *Muscinæ,* contains a number of genera that are of importance: *Stomoxys; Glossina; Musca; Auchmeromyia; Cordylobia; Calliphora; Lucilia; Compsomyia;* and *Pycnosoma.*

In the genus *Stomoxys* are the stable flies, of which *Stomoxys calcitrans* readily bites man. It resembles *Musca domestica;* but is readily distinguished by the proboscis, which is adapted for biting. The bite is painful, as the proboscis is large; but it leaves only a little redness, which soon disappears. *Stomoxys calcitrans* is accused of transmitting anthrax and trypanosomiasis in lower animals; and it has been accused of transmitting disease in man, but nothing definite is known regarding it.

In the genus *Glossina* are the *tsetse-flies* of Africa. *Glossina morsitans* is the transmitter of nagana in lower animals, and of Rhodesian trypanosomiasis in man. *Glossina palpalis* transmits human trypanosomiasis, in Africa, except in Rhodesia.

In the genus *Musca* is the common *house-fly* or *typhoid fly, Musca domestica.* This fly is found throughout the world, and because of its close association with man, it serves as the transmitter of a number of pathogenic organisms.

The male is from 6 to 6.5 mm. (1/4 inch) long; the female is from 6.5 to 7.5 mm. (1/4 to 3/10 inch) long. The head is dark, with a velvet-black frontal stripe. The scutum is gray, and has four longitudinal black stripes. The abdomen is yellow, with a median dark stripe and a dark tip. In the male, the eyes are nearly contiguous; in the female they are wide apart.

EVOLUTION.—*Musca domestica* prefers horse manure in which to deposit the eggs; but it will deposit its eggs in human excrement, house refuse, decaying vegetation, rubbish, and paper, and about garbage cans.

The eggs are from 0.8 to 1 mm. (1/30 to 1/25 inch) long, are cylindrical in shape, are creamy-white in color, shiny, and sticky. The female deposits several hundred eggs in a batch, and will deposit several batches; so one fly will deposit from 2,000 to 2,500 eggs during her life.

The eggs hatch in one day, under favorable temperature conditions, giving rise to a whitish larva (maggot). The larva has twelve segments, molts three times, and grows to be from 10 to 12 mm. (2/5 to 1/2 inch) in length. The larva is full grown in about seven days, when it leaves the food and crawls away to a dry place to pupate. It contracts to a long barrel-shape; the skin becomes smooth, hard and dry, and changes to dark-brown in color. This dried skin forms a shell, the *puparium,* and the organism is the *pupa.*

The pupal stage lasts about three days, when a circular piece is split off the head end of the puparium, the fly emerges, and waits for the wings and legs to harden so that it can fly. The flies copulate soon after emerging from the puparium, and the female begins to deposit eggs as soon as two days after she emerges. Thus, under favorable conditions, the entire cycle, from egg to egg, takes about thirteen days.

Breeding and Feeding Habits.—*Musca domestica* deposits its eggs in decomposing material, and its preference for horse manure leads it to deposit its eggs about stables, especially in camps. It will also deposit the eggs in human excreta in latrines and privies, and in any decaying material. A favorite place is in ground soaked with greasy water, about slop-cans, the kitchen door and incinerators. The ground about slop-cans may be firm, smooth, and shining with grease: half an inch below the surface, the ground may teem with fly larvæ.

As the larva becomes full grown, it leaves the food and travels to a dark, dry place to pupate, and it is important to know that the larva can travel long distances in the soil, and that the fly, when it leaves the pupa-case, can travel long distances through the soil—provided the soil is not too firm—to emerge in the ordinary way. Thus, when fly-larvæ are buried four feet in sand, the flies will emerge in the normal way; when fly larvæ are buried six feet deep in sand, a large percentage of the flies will emerge. Fabre watched flies come to the surface after emerging from the pupa-case; as the fly is ready to escape from the pupa-case, a hernia appears between the eyes, and bursts off the lid of the case; inflation and deflation of the frontal knob continues, and with these piston-strokes pushing the sand aside, and the legs pushing the displaced sand back, the fly emerges at the surface. As the larva travels away from the light, and the fly can travel a long distance through the earth, it is at once evident that it is useless to throw a little dirt over the ground containing fly larvæ, or even to bury the dirt containing larvæ.

A few adult flies pass through unfavorable seasons, such as winter, and in warm places, as in greenhouses, flies may breed all winter. But by far the most important way of passing through unfavorable seasons is in the pupal stage, less commonly in the larval stage. Pupæ and larvæ pass the winter in heaps of manure, just below the frozen portion, and, with the first warm days in the spring, the adult flies emerge. It is probable that the pupæ will live a long time in decaying rubbish, when such refuse is used for filling in low areas and is covered deeply with earth. When the earth is dug up, as in excavating for buildings, these pupæ hatch, and it is probable that this accounts, in part at least, for the scourge of flies sometimes noted when excavating for buildings on filled land.

Musca domestica is unable to bite, and it is unable to feed on solid food; the food must be in solution or suspended in a liquid in order that the fly may suck it in. The proboscis is fleshy, the mouth-parts are fused, and the labellæ are large and have a number of channels on their distal surface, these channels running to the canal through the proboscis.

The digestive ability of the house-fly makes for its adaptation as a transmitter of diseases. The adult fly can digest carbohydrates and partly digested protein material; and it obtains the carbohydrates from the food of man, and the partly digested protein from fecal material. In order to have the food in solution or suspended in a liquid, the fly regurgitates a drop of fluid from the crop onto the food, and then sucks up the drop of fluid with the dissolved or suspended food. If a fly is fed on fluid containing some coloring matter, and is then allowed to feed on a lump of sugar, the sugar around the spot where the fly is feeding will be stained with dye.

Another peculiarity of many arthropods is the tendency to frequent defecation when feeding. Thus, a fly will defecate as often as every five minutes when feeding, and material taken in through the proboscis may be passed by the feces within five minutes.

The fly, in feeding, walks on the fecal material, and then walks on the food, by means of its hairy legs transferring numerous bacteria from the feces to the food.

PATHOGENIC RÔLE.—The feeding habits of the house-fly render it especially adapted to transmitting organisms from the feces to the food of man, and it is in this connection that the house-fly has won its unenviable reputation.

The frequency of carriers of *typhoid* and *paratyphoid* bacilli makes it probable that any privy or latrine will contain these organisms. The flies walking on the feeding on such contaminated fecal material, and then walking on, regurgitating on, and defecating on, the food, are of great importance in the spread of these infections. To a lesser extent they spread *dysentery* and *cholera* organisms in the same way.

In Egypt, a purulent ophthalmia is common, and it is spread by flies. The flies there will fly directly at the eyes; and it is common for people to carry fans of various sorts to keep the flies away from the face.

Because of its breeding habits, the house-fly is not likely to deposit the eggs about the human body, and the larvæ are not apt to be taken into the stomach. But there are occasional cases in which the house-fly has deposited the eggs in the eyes of children suffering from trachoma, and in a few cases children have taken the eggs or larvæ into the digestive tract. It is not uncommon to see fly larvæ in the diapers of poorly-cared for children, and under such conditions they are apt to be mistaken for worms. The larvæ may pass through the anus into the rectum.

PROPHYLAXIS.—Protection from flies consists in (*a*) prevention of breeding; (*b*) destruction of flies, and (*c*) prevention of their gaining access to food.

1. *Prevention of Breeding.*—As flies breed in horse manure, in human excreta, and in decaying refuse of various kinds, preventing breeding consists in the destruction of such material, or in so protecting it or treating it that flies cannot breed in it.

(*a*) *Horse Manure.*—Flies deposit eggs only in fresh horse manure —usually not over twenty-four hours old; and they do not deposit their eggs in manure in which one batch of larvæ has been bred.

(i) *Incineration.*—Incineration of horse manure is an ideal method of preventing fly-breeding; but it is difficult to carry out, and is expensive, since, aside from the expense for care and fuel, the manure has a decided value as a fertilizer.

(ii) *Spreading.*—Spreading the manure is a satisfactory method in some localities. In dry regions, the manure may be spread in a thin layer on the ground, and allowed to dry; as soon as this layer is dry, another layer may be placed over it. But this method cannot be used in wet regions. The manure may be spread on the fields where it is intended to be used as fertilizer, as fast as it is produced; but in regions with the average amount of rain, the manure must be spread very thinly and evenly or it will serve for fly-breeding. If the manure cannot be removed as produced, it should be kept in fly-proof bins until removed.

(iii) *Close Packing.*—This consists in packing the manure in a compact heap on an area of firmly-packed ground. As each day's manure is added to the heap, it is packed down, moistened, and smoothed off. It is necessary to keep the manure firmly packed and moist, so that the fermentation will kill fly-eggs and larvæ.

(iv) *Maggot Traps.*—Such traps consist of a slatted platform, built over a shallow pit of concrete. The manure is thrown on the platform, and the pit is filled with water to a depth of one inch. The water should be covered with a film of oil, to prevent mosquito-breeding. Advantage is taken of the fly larva's habit of migrating when it is ready to pupate. When the larvæ are full-grown and attempt to leave the manure, to pupate, they fall through the platform into the water and are drowned. The pit is so arranged that it can be emptied and flushed out with water once a week.

(v) *Chemical Treatment.*—The United States Department of Agriculture has tried a number of chemicals, with the idea of preventing flies breeding in manure, without lessening the fertilizer value of the manure. *Hellebore* is one of the best chemicals for use in prevention of fly-breeding in manure, as it does not affect the fertilizing value of the manure. One-half pound of powdered hellebore is stirred in ten gallons of water, and is allowed to stand for twenty-four hours. This mixture is sprinkled over the manure, ten gallons of the mixture being used for 10 cubic feet of manure.

Borax is satisfactory, when used in amounts of one pound to 16 cubic feet of manure; but excess of borax may have an injurious effect on vegetation when the manure is used as fertilizer. The borax is best sprayed in solution over the manure; or, if it is applied in powder form, water should be sprinkled over the manure. Borax solution sprayed over the stable floor also assists in preventing the breeding of flies in the cracks of the floor and under the floor.

A mixture of **calcium cyanamid** and **acid phosphate** is satisfactory when applied at the rate of one-half pound of each for each bushel of manure. As these substances are of value as fertilizers, their use adds to the fertilizing value of the manure.

(*b*) *Human Excrement.*—Proper disposal of human excrement is necessary, not only to prevent flies from breeding in it, but also to prevent flies from feeding on it and carrying pathogenic microörganisms to the food.

A *water carriage system* is the most satisfactory method of disposing of human excrement; but in rural communities, small towns, and camps, such a method of disposal is generally not available, and the material has to be disposed of in privies and latrines. Privies and latrines should be made fly-proof, and the accumulated material disposed of by burning, discharging into a sewer, or burying. Care must be observed that the material is not disposed of in such a manner that it can contaminate drinking water. For a discussion of the methods of disposal in civilian communities, reference should be made to the publications of the United States Public Health Service, while for a discussion of the methods of disposal in camps, reference should be made to text-books on military hygiene.

(*c*) *Garbage and Other Waste.*—Such waste should be collected in fly-proof cans, and so disposed of that flies will not gain access to it. Garbage-cans should be scrubbed frequently, and the ground about them should not be soiled.

2. *Destruction of Flies.*—Flies may be caught in traps or on sticky fly-paper, killed with fly-swatters, and by poisons. Many of the fly-poisons contain arsenic, and are not without danger about the house. The United States Public Health Service found that a 1 per cent. solution of sodium salicylate is an efficient fly-poison when placed in saucers about the house, and when other liquids are removed from the room. **Formalin** (1 part of commercial formalin in 40 parts of water, and sweetened) is a satisfactory fly-poison. For practical purposes, three teaspoonfuls of sodium salicylate or formalin may be dissolved in a pint of water; a glass is then filled with the solution, and inverted over a sheet of blotting paper in a saucer, with a match placed under the edge of the glass at one side.

3. *Protection of Food.*—Houses should be screened, and all food should be kept in containers to which flies cannot gain access.

In the genus *Auchmeromyia* (*"sunburnt"* or *"dirty"* flies), the second abdominal segment is long. *Auchmeromyia luteola* is found in Africa. The larva is the *Congo floor maggot.* The adult fly deposits her eggs in cracks in the dirt floor of huts. The larvæ live in the cracks of the dirt floor beneath the sleeping mats, and come out at night to suck the blood of the persons who sleep on the mats.

Choeromyia is a related genus in Africa; and the larvæ of some species suck the blood of hairless animals, and may bite man.

Cordylobia resembles Auchmeromyia, but the second abdominal segment is not unusually long. *Cordylobia anthropophaga* is the *tumbu-fly* of Africa, and the larva is the *cayor maggot.* The adult fly lives on decomposing material, and the larva lives under the skin of rodents, especially rats and mice. It very often lives under the skin of dogs, less commonly under the skin of cats and goats. It is not infrequently found under the skin of man. Each larva causes a furuncle-like area of inflammation, in the center of which is an opening through which the maggot breathes. A number of these areas, each containing a maggot, all in the same stage of development, may be found in the same person.

It is not known how the larva gets under the skin. In the case of natives, it is thought that the larva gets into the skin of persons sleeping on the ground; in the case of whites, it is thought that the fly deposits the eggs on woolen clothing hung out to dry.

The larva is full grown in about seven days, when it comes out of the furuncle and falls to the ground to pupate; the adult fly emerges from the pupa-case in from fifteen to twenty days.

The genus *Calliphora* includes the *blue-bottle* or *blow-flies.* They are blue-black or metallic blue in color.

Calliphora erythrocephala and *Calliphora vomitoria* are the common blow-flies. They are attracted to decomposing meat, and the female deposits from 500 to 600 eggs, 1 mm. (1/25 inch) long, in such meat. The larvæ live in decomposing meat, and may be taken into the digestive tract of man by eating meat in which the fly has deposited her eggs (fly-blown meat). The fly may deposit her eggs in wounds in man and lower animals, and the larvæ (maggots) develop in the wound. The larvæ of Calliphora have been found in the nasal fossæ of man in Chile.

Phormia regina is the *black blow-fly.* It deposits its eggs especially in suppurating wounds, and causes myiasis of wounds.

The genus *Lucilia* includes the *green-bottle flies.* They resemble Calliphora in habits; but they are brilliant metallic or bluish-green in color. *Lucilia cæsar* is one of the commonest of the green-bottle flies in Europe and America. *Lucilia sericata* and *Lucilia cæsar* are the *sheep-maggot flies* in the United States. The female deposits her eggs in the soiled wool of the sheep, especially of those suffering from diarrhea. The maggots live under the matted wool, next to the skin, or burrow under the skin, especially through wounds caused by ticks or in other ways.

The larvæ of *Lucilia sericata* and *Lucilia cæsar* may cause cutaneous myiasis in man. Dyer and King, in New Orleans, report a case of myiasis of the feet and legs, due to the larvæ of *Lucilia sericata.*

Lucilia serenissima is a common bazar fly in South India, feeding on the meat exposed for sale.

In the genus *Chrysomyia,* the thorax is metallic green, with three longitudinal black bands. *Chrysomyia macellaria* is the *screw-worm fly* of Texas, Central and South America. The name "screw-worm" refers to the arrangement of the rows of spines on the segments of the larva: On the dorsal surface the four rows of spines are on the anterior border of the segment; but on the sides, the anterior two rows of spines pass forward to the posterior border of the segment in front, and are so arranged on the ventral surface, giving the appearance of the threads of a screw.

The eggs are deposited in decaying flesh, and the full-grown larvæ burrow in the ground to pupate.

Persons who have nasal catarrh, or who have unclean wounds, or are unclean from vomitus, are apt to be attacked by the female fly, the eggs being deposited in the nasal fossæ or in wounds. In their development, the larvæ destroy the flesh and bones, and there is commonly marked secondary infection with pus-producing bacteria.

The genus *Pycnosoma* includes blue or green flies, found in Asia and Africa. The larvæ may get into wounds.

Anthomyiidæ.—The family Anthomyiidæ, or flower flies, resemble the *Muscidæ,* but are distinguished by the wing venation. The eggs are deposited on plants, the larvæ being parasitic on the plants and doing much damage to vegetables, as onions, turnips, and radishes. The larvæ of some species are parasitic on insects, and others are parasitic on animals.

Fannia canicularis, the *lesser house fly,* is smaller than the common house fly, and is distinguished by the wing venation. This fly is frequently seen about the room and on the windows. *Fannia scalaris* is a common *latrine fly,* and is especially attracted by urine. It may deposit its eggs about the anus and genitalia. The larvæ of *Fannia canicularis* and *Fannia scalaris* are frequently taken into the digestive tract of man with fruit and vegetables, and they are among the commonest larvæ found in *intestinal myiasis,* often persisting for a period of years, if the person does not change the habits of eating. The larvæ of *Fannia scalaris* are the ones most commonly found in myiasis of the urinary passages.

Phoridæ.—Of the Phoridæ, *Aphiochæta ferruginea,* a small fly, is of interest in the tropics. This fly breeds in excrement, and is frequently seen around fresh meat. The fly is said to live in the human intestine, and to deposit eggs there, so the adult fly, larvæ, and eggs are all passed together in the stool.

Sarcophagidæ.—The family Sarcophagidæ, or *flesh flies,* are medium-sized to large, thickest flies. Many of the sarcophagidæ are viviparous, the female depositing small maggots, one after another, up to ten or more.

The larvæ are deposited in decaying meat; they may also be deposited in wounds, or in the nasal cavities, or they may be taken into the digestive tract with meat. The larva of the flesh flies resembles the larva of the screw-worm fly in structure, but the spines are minute. The destruction of tissue by the flesh-fly larvæ is as great as that by the screw worms.

Sarcophaga carnaria is the common gray and black flesh fly. Fabre has shown that this fly will drop her larvæ through a screen placed over meat, and will drop the larvæ as much as twenty-five inches onto meat. He points out that gauze screens will not protect meat from the larvæ of the flesh fly, also that the flesh fly will not deposit her larvæ, and the blue-bottle fly will not deposit her eggs, on paper closed tightly about a piece of meat, unless there is an opening through which the larvæ can reach the meat. Fabre also showed that the blow-flies and flesh flies will not deposit the eggs or larvæ when the meat is covered by an inch of sand, unless the meat-juice has soaked through to the surface of the sand. From this, he concludes the fly larvæ play no part in the disintegration of the body when buried.

The larvæ are frequently deposited in wounds and ulcers, in the vagina, and in the eyes in purulent inflammation. They may be taken into the intestinal tract with meat.

Wohlfartia magnifica is a common fly in Russia, and it frequently deposits the larvæ in wounds or in the nasal fossæ. It infested wounds on the western front in the recent war, especially during 1915. Walker reports the finding of the larvæ of *Wohlfartia vigil* in boil-like sores on two infants in Canada.

Oestridæ.—The family Oestridæ, or *bot-flies,* are bee-like, more or less hairy flies, with a large head and a heavy, swollen face. There are three ocelli between the eyes. The mouth is small, and the mouth-parts are rudimentary. The adults are very short-lived. The larvæ are stout, and the segments bear rings of many large, dark-colored spines.

The oestridæ attach the eggs to the hairs of animals, the larvæ being parasitic in these animals, either in the digestive tract, the naso-pharyngeal spaces, or in the subcutaneous tissues. When the maggot is full grown, it leaves the host and falls to the ground to pupate.

Each species of bot-fly has a preference for some particular animal, and a number of them are parasitic in domestic animals. A few of them may infest man.

In the genus *Gastrophilis, Gastrophilis hemorrhoidalis,* the *red-tailed bot-fly,* is a common bot-fly of the horse. The eggs are deposited on the hairs of the horse, are licked off by the animal, and the larva lives in the stomach of the horse. The full-grown larva is passed in the feces and pupates on the ground. This fly will deposit its eggs on the hair, eyelashes and eyebrows of man, and the larva is one of the causes of *creeping eruption.*

Gastrophilis intestinalis is the most common bot-fly of the horse, and the larvæ may cause *cutaneous myiasis* in man.

Gastrophilis nasalis is the *chin fly* or throat *bot-fly* of the horse.

In the genus *Oestrus, Oestrus ovis* is the common bot-fly of sheep, and the larva is the *sheep-head maggot.* The larva lives in the nasal cavities of the sheep, the full-grown larva falling to the ground to pupate. This fly may deposit her larvæ in the eyes, ears, nose, or mouth of man. *Rhinoestrus nasalis* is a closely related fly, the larvæ living in the nasal cavities of the horse. The larvæ of these flies may be deposited in the eyes, nasal cavities, or mouth of man. *Rhinoestrus purpureus* is a related fly, attacking horses in Russia; and the larvæ may be deposited in the eyes of man.

In the genus *Hypoderma, Hypoderma bovis* and *Hypoderma lineata* are the common bot-flies, *warble flies, heel flies,* of cattle. The eggs are deposited on the hair, and it is generally held that they are licked off by the animal, hatch in the stomach, and pass to the subcutaneous tissues, where they form inflammatory tumors. Bishopp says that the larvæ generally go through the skin, but may be licked off the hair and taken into the stomach. The full-grown larva crawls out through an opening in the skin, and falls to the ground to pupate. The larvæ may be found in the subcutaneous tissues of man, where they are causes of creeping eruption.

The genus *Dermatobia* are American flies, found in tropical America and the West Indies. The larvæ live in the subcutaneous tissues of lower animals—especially cattle—and in man. In *Dermatobia cyaniventria* (*hominis*) the adults are metallic blue and gray in color. The life history is a little peculiar. The adults live in the woods about the pastures in South America, and deposit the eggs in masses on the under-side of leaves on the branches of trees. The eggs are sticky, and when a mosquito (*Janthinosoma lutzi*) lights on the leaves, the eggs stick to the mosquito. The fully-developed larvæ lie dormant in the egg until the mosquito bites an animal; the warmth of the animal makes the larva leave the egg, when it transfers to the skin of the animal, penetrates the skin, and develops in a local inflammatory mass as the *macaw worm.* The larva is found in cattle, dogs, and man. It remains in the skin from two to six months, the full-grown larva falling to the ground to pupate.

Dunn is of the opinion that this larva is transmitted by ticks as well as by mosquitoes.

(*a*) *Pathogenic Action of Fly Larvæ*

The larva of *Auchmeromyia luteola* is the *Congo floor maggot,* which sucks the blood of man; but the bite is not painful, and the larva is not known to transmit any disease.

Infestation with fly larvæ is known as *myiasis.* Fly larvæ may live in man as obligatory parasites, as facultative parasites, or as accidental parasites. The obligatory parasites cause *cutaneous myiasis;* the facultative parasites cause *myiasis of wounds,* the *natural cavities* and the *intestinal tract.* The accidental parasites usually occur in the intestinal tract.

(*i*) *Cutaneous Myiasis*

Cutaneous myiasis is the condition caused by the development of fly larvæ as obligatory parasites in the skin or subcutaneous tissues.

There are different clinical varieties of cutaneous myiasis; but it is convenient to distinguish three types:

1. Larva migrans, or creeping eruption.
2. Phantom tumors.
3. Furunculous myiasis.

Larva Migrans.—The condition begins as a small, painful area in the subcutaneous tissues. This painful point moves about continuously, its path being indicated by a red line. Vesicles may appear over the path of the larva. The larva travels from a fraction of an inch to two or three inches a day, often being more active at night. The head end of the larva may be seen as a dark speck, at the advancing end of the red line, especially when a piece of glass is pressed down on the area, and a magnifying glass is used for examining.

When the larva is ready to come out and pupate, a small tumor appears at the site of the painful point, the tumor opens at the top, and the larva and a seropurulent fluid escape.

The condition is caused by the larva of *Hypoderma bovis*, *Hypoderma lineata*, *Gastrophilis*, and *Gastrophilis hemorrhoidalis*. The eggs of the fly may be found attached to the hair in the region of the eruption.

Phantom Tumors.—In this form of myiasis, a subcutaneous painful area is accomplished by the development of a red, edematous area. After persisting for a few days, this area disappears, to appear somewhere else. After three or four months, a furunculous tumor appears, opens at the top, and the larva comes out.

The condition is caused by the larvæ of *Hypoderma bovis* and *Hypoderma lineata.*

Furunculous Myiasis.—In this form of myiasis, the cutaneous tumor is the first and last indication of the disease. Either the larva develops at the site where it entered the skin (Cayor maggot and macaw worm), or the maggot emigrates through the tissues without causing any symptoms until it arrives at the place where it is to come out (*Hypoderma bovis*).

At times, the wound left by the escape of the larva becomes infested with the larvæ of some of the blow-flies, as *Chrysomyia macellaria*, or some of the flesh flies.

In man, it is probable that the larva of Gastrophilis hatches from an egg deposited on the hair, near the skin, and passes down a hair follicle and through the skin to the subcutaneous tissues. But Bishopp thinks that Gastrophilis larvæ go through the mucous membranes, as the lips or conjunctiva. Haematobia eggs, taken into the stomach, hatch there, and the larva travels through the tissues to the subcutaneous tissues. Dermatobia larvæ develop in the skin and subcutaneous tissues at the point where they are deposited by mosquitoes or ticks. The Cayor maggot develops in the skin at the point at which it first gains entrance.

(*ii*) *Myiasis of Cavities*

This condition is caused by the development of fly larvæ as facultative parasites in wounds and in the natural cavities of the body.

In myiasis of the *nasal cavities,* the larvæ destroy the mucosa of the nose, and continue through the other tissues, even bones. There is often severe secondary bacterial infection.

Myiasis of the *auditory canal* occurs only in persons with some disease of the ear.

Myiasis of the *conjunctival sac* is usually secondary to nasal myiasis, although *Oestrus ovis, Rhinoestrus nasalis* and *Rhinoestrus purpureus* may deposit the larvæ in the eyes.

In myiasis of the *bladder,* the eggs are deposited about the genitalia, and the larvæ enter the bladder through the urethra. The larvæ may enter the *vagina* in the same way. The larvæ of *Fannia scalaris* are the ones most commonly found in myiasis of the bladder.

It is not uncommon for several of the natural cavities to be infested with fly larvæ at the same time.

Myiasis of *wounds* results from the development of fly larvæ in wounds and ulcers. *Lucilia sericata, Lucilia cæsar, Lucilia regina,* and various species of *Sarcophaga* and *Pycnosoma* may deposit their eggs or larvæ in wounds or ulcers, and the wounds are enlarged rapidly as the fly larvæ develop. Fabre found that fly larvæ are able to liquefy proteins, but not fats, and he suggests that the liquefaction of protein results from a digestive fluid which the larva regurgitates. The buccal hooklets are used in locomotion, but not in feeding.

There have been a few cases of *generalized myiasis,* in which the eggs of flies were deposited all over a man; these were probably *Calliphora* and *Lucilia.*

(*iii*) *Intestinal Myiasis*

Intestinal myiasis is caused by the ingestion of fly larvæ or eggs, and their development, as facultative or accidental parasites, in the digestive tract. Larvæ may enter the rectum through the anus, from eggs deposited about the anus. House-fly-larvæ may enter the rectum of children in this way.

The larvæ are usually taken in with food, as in eating meat, fruit, vegetables, or cheese, containing fly larvæ. The larvæ rarely live; but when they do live, they produce varying symptoms, according to the part of the intestine in which they stop. If they stop in the stomach, they cause nausea, vomiting and pain; if they stop in the intestine, they cause colicky pain and hemorrhage, and if they remain in the intestine for some time, they cause a mucomembranous colitis or a severe enteritis.

Any fly-larvæ may be taken in with food, the rat-tail larva being among those most commonly found.

Diagnosis of Myiasis in General.—The diagnosis of myiasis is made on finding the fly larvæ.

Structure of a Fly Larva.—Fly larvæ are cylindrical, worm-like, and pointed at the anterior end. The body is segmented, and there are rows of spines on the segments. The narrow head-end bears two antennæ, and one, two or four buccal hooklets. The stigmal plates are in the posterior end of the last segment, and the tracheal openings are in these plates.

IDENTIFICATION.—It is necessary to distinguish fly larvæ from worms. The antennæ, buccal hooklets, stigmal plates, and rows of spines on the segments serve to distinguish fly larvæ from worms. None of the worms that might be confused with fly larvæ are segmented.

When fly larvæ are obtained, they should be kept alive, and flies bred out from them, as it is difficult to identify flies by the larvæ. The stigmal plates are of great importance in the identification of different fly larvæ.

Treatment of Myiasis in General.—PROPHYLAXIS.—The Congo floor maggot is avoided by sleeping in **beds** or **hammocks**. The larvæ causing cutaneous myiasis are obligatory parasites, generally found in lower animals. Prophylaxis consists in preventing the development of these larvæ, and, as the condition is rare in man, and does little harm in man, the main reason for fighting these flies is to prevent the loss they occasion among domestic animals.

Prevention of myiasis of cavities and wounds consists in **preventing the breeding of flies** whose larvæ cause the condition, and in avoiding attack by them. Carcasses of dead animals should be burned, buried, or treated with chemicals, promptly, so that flies cannot breed in them. **Garbage**—especially meat scraps—should be **disposed of**, and flies should be destroyed as indicated in discussing the house-fly. **Creosote and cresol** solutions act as fly repellants, when used for washing places frequented by flies.

All **wounds** should be **kept clean** and dressed, and hospitals should be **screened**. Persons—especially if they have nasal catarrh—should avoid sleeping in the open during the hours when flies are active. Fly larvæ gain access to the genito-urinary passages from eggs deposited about the genitalia, as in latrines or in sleeping in the open air.

Great care is necessary in eating fresh vegetables and fruits, that fly-eggs or larvæ are not taken in with the food. The rat-tail larva, one of the larvæ commonly causing intestinal myiasis, is frequently taken in with improperly washed water cress and lettuce. Fly-larvæ gain access to the rectum from eggs deposited about the anus, as in latrines or in sleeping in the open air, or, as in children, from eggs deposited in soiled diapers.

GENERAL TREATMENT.—Fly-larvæ do not multiply in the body, and one of the Phoridæ—in which the adult fly can live in the human intestine, and can deposit the eggs there—is the only adult fly which is known to live in the human body. Therefore, one of the first steps in treatment of myiasis is to determine the source of the fly-larvæ and to see that no more larvæ gain access to the body.

In cases of *creeping eruption,* the larva does no harm, other than the slight pain due to its migration, and the mental disturbance of the patient and his friends, and, if undisturbed, it comes out in a few days and falls to the ground to pupate.

Various substances have been injected into the area occupied by the larva, at the advancing end of the red line, a few drops of **chloroform** probably being the most satisfactory. The larva may be removed by making a flap-like incision in front of it, and extracting it from the upturned flap. It is necessary to use a magnifying glass to locate the larva, and it is found a little in advance of the end of the red line.

In *phantom tumors,* it is advisable to allow the larva to come to rest, and then the larva is removed as in furunculous myiasis.

In *furunculous myiasis,* the posterior end of the larva is usually seen through an opening in the furuncle-like swelling. The larvæ may be grasped with forceps and removed; or a few drops of chloroform may first be injected into the larva.

In *myiasis of the nasal cavities,* it is advisable to **remove** as many as possible of the larvæ by picking them out with forceps. Then **chloroform** is inhaled, and the cavities are flushed with **boric acid solution** or physiological **salt solution.** Or the cavities may be flushed with chloroform water. Jeanselme and Rist advise injection of pure **benzin** into the cavities, and Stiles advises washing with 20 per cent. **chloroform in sweet milk,** or with a **phenol** solution. After-treatment consists in keeping the cavities clean with a bland solution.

In *myiasis of the auditory canal,* after **mechanical removal** of as many as possible of the larvæ, the ear is plugged for a short time with cotton soaked in **chloroform,** and then flushed with physiological **salt solution** or **boric acid solution.**

In *myiasis of wounds,* after **mechanical removal** of as many as possible of the larvæ, the wound is treated as advised by Stiles and by Jeanselme and Rist for myiasis of the nasal cavities. Flushing the wound with **magnesium sulphate** solution would seem to be advisable. The **wound** should be **kept clean** and dressed.

Myiasis of the bladder is treated by irrigation with **chloroform water.** Irrigation with magnesium sulphate solution should be serviceable here.

Intestinal myiasis is treated by the use of **vermifuges** and **purgatives. Pumpkin-seed** has been used with satisfactory results. **Oil of Chenopodium** and **thymol** should be used as for intestinal worms. Quite frequently it is not possible to remove all the larvæ from the intestinal tract; but the few that remain do no harm, and are soon passed out.

When the larvæ are in the rectum, enemata of **creolin,** 1 to 250 solution, or of magnesium sulphate solution, may be used. Hall gave a rectal injection of 1 c.c. of chloroform in 9 c.c. of olive oil to a dog with rectal myiasis. At postmortem examination, the next day, the rectum was found to be free from larvæ, and there were a few dead larvæ higher up in the intestine.

Prognosis of Myiasis in General.—Cutaneous myiasis is not dangerous, as the larva comes out in from a few days to a few months, without doing any damage.

Myiasis of cavities and wounds is dangerous, on account of the destruction of tissue, the danger of bacterial infection, and hemorrhage. Meningitis may result from myiasis about the head. Barlara reports a case of fatal hemorrhage from the nose and mouth, following myiasis that was apparently cured.

Intestinal myiasis is not dangerous, though, if prolonged, it may lead to chronic enteritis or chronic colitis.

(3) *Suborder: Nematocera*

The Nematocera are characterized by their long antennæ, having from six to fifteen segments. The body is slender, and the wings are long and slender. The larvæ generally live in water, but may live in moist earth or in decaying vegetation.

The wings vary greatly in the Nematocera, the wing venation being of great importance in classification.

Simulidæ.—The family Simulidæ are the "*buffalo gnats,*" "*turkey gnats*" or "*potu flies.*" They are sometimes called sand-flies. The body is thick, and the back is humped. The antennæ are cylindrical, rather short, and have ten segments. The palps are short, and have four segments.

The proboscis is short and stumpy. The mouth-parts are the same as in the female tabanid. The labium is fleshy, with large labellæ; the epipharynx is armed at the tip with recurved hooklets, and is grooved on the ventral surface; the hypopharynx has a canal through it; the mandibles and maxillæ are lancet-shaped, and serrated on the edges.

When the gnat bites, the mandibles and maxillæ cut the way; the epipharynx and hypopharynx are approximated to form the blood-tube; and the saliva is injected through the canal in the hypopharynx.

The Simulidæ are found in all parts of the world. The females are blood-suckers, biting by day; but they do not enter houses. These gnats appear in swarms, generally near streams where there are woods. They rest on the under surface of the leaves, near the ground.

The story of the life-cycle reads like a fairy tale.

PATHOGENIC RÔLE.—Simulia attack lower animals and man; they often go in swarms, and cause great distress and even death to lower animals. The bite produces a sharp stinging sensation, and at the site of the bite there is frequently a tiny drop of blood in the skin, surrounded by an erythematous area.

Simulia are not known to transmit any disease. Robles says that simulia are the only biting flies in the region in which *Onchocerca volvulus* infection is found in Guatemala, and that the distribution of the flies corresponds to the distribution of volvulus infection there.

Chironimidæ.—The family Chironimidæ includes the small midges which are so commonly seen about lights in the tropics, especially during the rainy season. They also dance over water, in swarms. They are common near water, and in undergrowth. They may be found on the windows of houses, and are frequently mistaken for mosquitoes. The mouth-parts are the same as in simulium.

The family is an enormous one, and is divided into five subfamilies, one of which (*Ceratopogoninæ*) contains blood-sucking forms. The genus *Culicoides* contains many biting species in various parts of the world. They are known as *punkies*, and, on account of their small size, they are known to some of the Indians as *no-see-ums*. In some places they are known as sand-flies.

PATHOGENIC RÔLE.—The bite of the female of the Ceratopogoninæ is very irritating. They are not known to transmit any disease.

Psychodidæ.—The family Psychodidæ are small, hairy, moth-like gnats, known as *owl-midges*. The entire body is covered with hairs, but there may be some scales on the wings.

The genus *Phlebotomus* contains the only blood-suckers in the family, these being the true *sand-flies*. In phlebotomus, the proboscis is long, and the mouth-parts are like those of simulium. The females are blood-suckers, biting man and lower animals. They especially like to suck the blood of snakes and lizards, and they are commonly seen attached to such animals. The males generally do not bite.

PATHOGENIC RÔLE.—The females will work their way through or under a mosquito-net, and the stinging bite, followed by intense itching, makes them a great nuisance.

Phlebotomus papatasii transmits *phlebotomus fever*. Townsend considers that a phlebotomus (*Phlebotomus verrucarum*) is the transmitter of *Verruga peruviana* in Peru. He considers that a lizard is the reservoir for the virus. The work has not been confirmed.

Culicidæ.—The family Culicidæ includes the mosquitoes. Theobald has written a five-volume monograph on the mosquitoes of the world, and Howard, Dyar and Knab have written a four-volume monograph on the mosquitoes of North and Central America and the West Indies. For extensive consideration of the subject, one should consult these works or the other works mentioned in the list of references.

The family is usually divided into three subfamilies: *Dixinæ, Corethrinæ,* and *Culicinæ*. The Dixinæ and Corethrinæ are of interest only on account of the danger of confusing them with the Culicinæ, or mosquitoes.

The *Culicinæ,* or mosquitoes, are long and slender, and the entire body and wings are clothed with characteristic scales. The proboscis is long, and in the female is well adapted for piercing; in the male it is simple and not used for piercing. The antennæ are long, with fourteen joints in the female and fifteen joints in the male. The palps have four joints, and may be long or short in both sexes, or long in one sex and short in the other. The wing venation is characteristic.

This subfamily contains over 1,200 species, and many of the females are blood-suckers; the males feed on plant juices.

The proboscis is composed of the labium or lower lip, which forms a sheath, in the groove of which lie six stylets: two maxillæ, two mandibles, the epipharynx, and the hypopharynx. The paired maxillæ are tapering stylets, serrated at the end; they partly surround the other stylets and help to bind them together. Above the maxillæ are the mandibles, delicate, tapering stylets. Above the mandibles, in the median line, is the hypopharynx, a symmetrical, tapering stylet, with a longitudinal rib in the median line; the rib is tubular, forming the salivary duct. The epipharynx, consisting of the thin labrum fused with the epipharynx, is horseshoe-shaped, with the opening below, and tapering to a point. When apposed, the hypopharynx closes in the opening in the lower side of the epipharynx, and these two parts form the tube through which the blood is sucked. At the sides of the tip of the labium are two lobiform appendages, the labellæ.

When the mosquito bites, the labellæ are placed against the skin, to serve as a guide for the cutting parts, and the maxillæ and mandibles are used to cut an opening through the skin. As the cut is made, the apposed epipharynx and hypopharynx are passed down into the wound. The labium is not passed into the wound, but bends up in the form of a bow as the other mouth-parts are passed deeper and deeper into the wound. The saliva is injected down the tube in the hypopharynx, and the powerful pharynx pumps the blood up the tube formed by the apposition of the epipharynx and hypopharynx.

EVOLUTION.—The eggs are deposited on the surface of water, or, as with some species of Aëdes, on ground where water frequently stands. At a favorable temperature; the egg hatches in two or three days. The eggs resist drying for some time; the eggs of *Aëdes argenteus* (*Stegomyia calopus* or *fasciata*) will hatch after having been kept dry for six months; Dunn, at Panama, hatched *Stegomyia scutellaris* from dirt that had been shipped from India.

The larvæ live in water, the larvæ of *Culex* and *Aëdes* floating at the surface of the water, with the tip of the respiratory tube thrust up to breathe, the body hanging obliquely, with the head down. The larva of *Anopheles* floats horizontally at the surface of the water, being supported by tufts of hairs on the dorsal surface of the abdominal segments.

The larva molts several times, and in about a week has completed its development, and changes to the pupa. It ceases to feed, and folds on itself to the shape of a question-mark, and two breathing trumpets appear on the dorsal surface. The pupa does not feed, but remains at the surface, with the breathing trumpets thrust up to breathe. When the pupa is distributed, it darts to the bottom by vigorous strokes with its abdomen and terminal "paddles."

Mansonia titillans is peculiar, in that the larvæ and pupæ do not come to the surface of the water to breathe, but live among the roots of water plants, with the breathing tubes thrust into the roots.

In three or four days, the adult mosquito emerges from the pupa-case. The males hatch first, and copulation takes place soon after the females hatch. The males die soon after copulation. Many, but not all, female mosquitoes require a feed of blood before they can deposit their eggs; the blood may be from any animal, and not necessarily from man. The female mosquito will deposit eggs in two or three days after a feed of blood.

Mosquitoes usually pass the winter and dry season in the egg. Some mosquitoes, as Aëdes, deposit the eggs on the ground, and they are hatched when the water comes, at times from the melting snow in the spring. Some eggs will not hatch until they have been submitted to freezing temperature.

Some mosquito-larvæ pass the winter in water, either frozen in the ice, or more commonly in the water beneath the ice, or in water which is not frozen but is too cold for them to continue their development.

Some mosquitoes pass the winter in the adult stage.

PATHOGENIC RÔLE.—When a mosquito bites, the irritating saliva is injected into the wound. Soon after the bite there is itching, and a wheal forms. The irritation from the bite of a mosquito varies in different people, and with different species of mosquitoes. In some persons there is no irritation, while in other persons the bite may swell and cause as much inconvenience as a bee-sting. Persons seem to acquire an immunity to the poison of some mosquitoes, so that the bite of one species causes no inconvenience, while the bite of another species causes considerable irritation.

TREATMENT.—Ordinarily the bite of a mosquito requires no treatment, but if the irritation is annoying, a dilute solution of **ammonia** may be applied, or **moist soap** may be rubbed on.

Application of a solution of from 2 to 2.65 grams (31 to 40 grains) of **iodin** in 30 c.c. (1 fluidounce) of **saponated petroleum** is said to relieve the irritation promptly.

The great importance of mosquitoes is in connection with their rôle as carriers of pathogenic microörganisms. *Malaria* is carried by Anopheles throughout the world. But by no means all of the species of Anopheles act as carriers of the malaria organism, and different species of Anopheles act as the carrier in different parts of the world. *Yellow fever* is transmitted by *Aëdes argenteus. Dengue fever* is transmitted by *Culex quinquefasciatus* and *Aëdes argenteus. Filariasis* is transmitted by *Culex quinquefasciatus, Mansonia uniformis, Stegomyia scutellaris,* and some species of *Tæniorhynchus. Janthinosoma lutzi* plays an important part in the transmission of *myiasis* due to *Dermatobia cyaniventris.*

PROPHYLAXIS.—The details of the fight against mosquitoes will depend upon the habits of the mosquito being fought, and for the details of the plan one should consult some of the works given in the list of references. The general plan will be divided into: (1) a fight against the *larvæ,* and (2) a fight against the *adults.* A great part of the work is *community work,* while a certain amount of *personal prophylaxis* can be carried out.

(1) *Larvæ.*—The eggs are deposited in different places by different species of mosquito: in tin cans, bamboo, flower-pots, fire-buckets, roof-

gutters, water-containers, cisterns, stumps, pools, streams, and marshes, and they may be deposited in fresh, brackish or salt water.

- (*a*) Destroy breeding-places
  - Draining.
  - Filling.
  - Cleaning and cementing banks of streams.
  - Removing or screening artificial water-containers.
  - Cleaning water-cabbage and such plants out of the water.

- (*b*) Destroy larvæ
  - Putting fish and insect-larvæ in the water.
  - Pouring oil on the surface, or some insecticide in the water.

(2) *Adults.*—The hiding places are destroyed or sprayed with oil, and rubbish and undergrowth is cleared away from around the houses. Mosquitoes in buildings can be destroyed by **sulphur fumigation,** or by fumigation with **pyrethrum** or **tobacco stalks.** After the pyrethrum and tobacco fumigation, it is necessary to sweep up the mosquitoes and **burn** them, or they will recover. Sulphur fumigation is usually employed for the destruction of mosquitoes in the holds of ships.

Individual prophylaxis consists in the **screening** of houses, sleeping under **mosquito nets,** wearing **head nets** and **gloves,** protecting the ankles with high shoes and long trousers or drawers, and the use of **repellants.**

Houses should be thoroughly screened with a non-corrosive wire screen, having not less than 16, preferably 18, meshes to the inch. It is not uncommon to see houses screened with screens of 14 or 15 meshes to the inch, and although the screens are in good condition, the mosquitoes readily enter the house through the meshes in the screens.

Citronella is one of the most commonly used mosquito repellants. **Kerosene** is satisfactory, and may be combined with some substance, as **oil of wintergreen** or **pennyroyal,** to overcome the odor. The various **pine-tar** products are satisfactory mosquito repellants. The repellant is rubbed on the face, neck, hands, and ankles; it requires renewing in a couple of hours. The various "**punk-sticks**" act as repellants when burned in a room.

REFERENCES

General Works

ALCOCK, A. Entomology for medical officers. Gurney and Jackson, London, 1911.

BRUMPT, E. Précis de parasitologie. Second edition. Masson & Co., Paris, 1913.

Castellani, A., and Chalmers, A. J. Manual of tropical medicine. Second edition. Wm. Wood & Co., New York, 1913.

Chandler, A. C. Animal parasites and human disease. John Wiley and Sons, New York, 1918.

Patton, W. S., and Cragg, F. W. A text-book of medical entomology. Christian literature Society for India, London, 1913.

Riley, W. A., and Johannsen, O. A. Handbook of medical entomology. The Comstock Publishing Company, Ithaca, New York, 1915.

Stelwagon, H. W. Treatise on diseases of the skin. Seventh edition. W. B. Saunders Company, Philadelphia, 1914.

Stiles, C. W. Diseases caused by animal parasites. Osler and McCrae's Modern Medicine, Second edition, ii, Lea and Febiger, Philadelphia, 1914.

Acariasis

Banks, N. The acarina or mites. Report No. 108, U. S. Department of Agriculture. Government Printing Office, Washington, 1915.

Grain Itch

Rawles, G. T. Dermatitis ditropenotus aureoviridis. Synonym, straw itch. Jour. Indiana State Med. Assn., Ft. Wayne, 1909, ii, 337.

Schamberg, J. F. Grain itch (acarodermatitis urticarioides): A study of a new disease in this country. Jour. Cutan. Dis., New York, 1910, xxviii, 67.

Schamberg, J. F., and Goldberger, J. Epidemic of an urticarioid dermatitis due to a small mite (Pediculoides ventricosus) in the straw of mattresses. Pub. Health Reports, Washington, 1909, xxiv, 973.

Ixodiasis

Cleland, J. B. Injuries and diseases of men in Australia attributable to animals (except insects). Australasian Med. Gaz., Sydney, 1912, xxxii, 295.

Easton, E. M. A case of tick-bite followed by wide-spread transitory muscular paralysis. Australasian Med. Gaz., Sydney, 1913, xxxiii, 391.

Hadwen, S. On "tick paralysis" in sheep and man following bites of Dermacentor venustus. Parasitology, Cambridge, 1913-14, vi, 283.

Hadwen, S., and Nuttall, G. H. F. Experimental "tick paralysis" in the dog. Parasitology, Cambridge, 1913-14, vi, 298.

Herms, W. B. The Pajaroello tick (Ornithodorus coriaceus Koch). Jour. of Parasitol., Urbana, Ill., 1915, ii, 137.

Moody, C. S. The wood-tick as a cause of paralysis. Amer. Jour. Clin. Med., Chicago, 1915, xxii, 1102.

Nuttall, G. H. F. "Tick paralysis" in man and animals. Parasitology, Cambridge, 1914-15, vii, 95.

Strickland, C. Note on a case of "tick paralysis" in Australia. Parasitology, Cambridge, 1914-15, vii, 379.

Temple, I. U. Acute ascending paralysis, or tick paralysis. Med. Sentinel, Portland, Oregon, 1912, xx, 507.

Todd, J. L. Does a human tick-borne disease exist in British Columbia? Canad. Med. Assn. Jour., Toronto, 1912, ii, New series, 686.

——— Tick bite in British Columbia. Canad. Med. Assn. Journ., Toronto, 1912, ii, New series, 1118.

Flies

Fabre, J. H. The life of the fly. Translated by A. T. de Mattos, 1916. Dodd, Mead and Company, New York.

Howard, L. O., and Hutchinson, R. H. The house-fly. Farmer's Bull. 851, U. S. Department of Agriculture, Washington, 1917.

LELAND, P. S. Sanitation in war. Second edition. Blakiston's Son & Co., Philadelphia, 1917.

PHELPS, E. B., AND STEPHENSON, A. F. Fly poisons. Pub. Health Reports, Washington, 1916, xxxi, 3033.

STIMPSON, W. G., AND FOSTER, M. H. Prevention of disease and care of the sick. Miscellaneous Publication No. 17, U. S. Public Health Service, Washington, 1919.

Myiasis

BARLARA, P. M. Sobre un caso de miasis, muerto por hemorrhagia. Prensa Méd. Argentina, Buenos Aires, 1919-20, vi, 54.

BISHOPP, F. C. Proceedings of the class formed to study the entomology of disease. Hygiene and Sanitation, Bureau of Entomology, Washington, 1918, 317.

DE ALMEIRA, T. Myiasis cavitaria e sue tratamento. Arch. Brasil. de med., Rio de Janeiro, 1919, ix, 496.

HALL, M. C. Myiasis due to syrphid larvæ. Arch. Int. Med., Chicago, 1918, xxi, 309.

WALKER, E. M. Wohlfartia vigil. Jour. Parisitol., Urbana, 1920, vii, 1.

Mosquitoes

HOWARD, L. O. Preventive and remedial work against mosquitoes. Bureau of Entomology, Bull. No. 88, U. S. Department of Agriculture, Washington, 1910.

———— Preventive and remedial work against mosquitoes. Bull. No. 88, Bureau of Entomology, U. S. Department of Agriculture, Washington, 1910.

HOWARD, L. O., DYAR, H. G., AND KNAB, F. The mosquitoes of North and Central America and the West Indies. The Carnegie Institution, Washington, 1912-1917.

LEPRINCE, J. A., AND ORENSTEIN, A. J. Mosquito control in Panama. G. P. Putnam's Sons, New York, 1916.

THEOBALD, F. V. A monograph of the Culicidæ, or mosquitoes. Longmans & Co., London, 1901-1910.

WATSON, M. Rural sanitation in the tropics. E. P. Dutton and Company, New York, 1915.

CHAPTER XLIX

INFLUENZA

By Hugo A. Freund, M.D.

Introduction, p. 275.
Definition, p. 276.
Etiology, p. 276:—Bacteriology, p. 279; Modes of transmission, p. 283; Immunity, p. 283; Prevention and contagion, p. 285.
Symptomatology and diagnosis, p. 286:—Period of incubation, p. 286; Mode of onset, p. 287; Course with gradual onset, p. 291; Physical examination, p. 295; Laboratory findings, p. 296; Convalescence, p. 297.
Complications, p. 298:—Bronchopneumonia, p. 298; Other complications, p. 301.
Treatment, p. 305:—Treatment of symptoms, p. 305:—General methods, p. 305; Drugs, p. 306; Hydrotherapy, p. 306—Cough, p. 307; Collapse, p. 307; Pain, p. 307; Diet, p. 308; Vaccine therapy, p. 308; Serum therapy, p. 308; Venesection, p. 308.
Pathology, p. 309.
Historical summary, p. 314.
Bibliography, p. 325.

Introduction.—To review the subject of influenza at the present time (1922) is essentially to write the history of the pandemic of 1918-1919-1920. Regardless of the opportunities that have presented themselves, additional knowledge acquired in respect to this disease has been largely of a negative character. The fact that the great nations of the earth were organized for war afforded possibilities for investigation, observation and statistical study. Not alone were victims of the disease in absolutely defined areas, but they were under such discipline as made their segregation, management and strict control possible. Furthermore, the medical profession, not alone that part of it thoroughly equipped for technical work, but also a group possessed of fine clinical ability, were mobilized. Their distribution throughout the camps and among the varied units of our fighting forces made for such systematic study and gathering of data as had never before existed. Even at this writing an immense amount of work is being done on all phases of influenza in the medical departments of the Army, Navy and Public Health Service. Besides this one cannot neglect recording the definite and sustained efforts continuously expended in institutions of research, in hospitals, boards of health, and individually by competent observers. Newer technic has afforded means for more critical scrutiny of the Pfeiffer and Beck bacteriologic work on influenza. The factors of the complicating pneumonias have been more definitely observed. Experimental studies on the contagiousness and modes of transmission were carried out, not alone among recruits in camps, but also through personal sacrifice in groups of individuals. This pandemic has run its course, The winters of 1919 and 1920 saw a recrudescence of the disease. Communities untouched during the great wave and susceptibles that escaped will serve as material for sporadic outbreaks for the coming and for a few subsequent years. As the subject stands to-day the chapter of this pandemic is practically closed. Yet little that was unknown has been unfolded. Save a few facts of epidemiology, the doubt cast upon the specificity of the *bacillus influenzæ* of Pfeiffer, the addition of certain immunologic and serologic observations, and the nature of certain complications, that which is written to-day must in a measure repeat the experiences of others who have lived through and observed the previous epidemics in history.

Definition.—Influenza is an acute, highly contagious infectious disease, occurring in pandemic, epidemic and isolated form. It is characterized by suddenness of onset, temperature, headache, marked prostration, respiratory symptoms and a tendency to severe pulmonary complications.

Etiology.—When R. Pfeiffer described the bacillus of influenza in 1892, an apparent advance was heralded in our knowledge of the disease. The determination of its cause opened great possibilities for the furtherance of studies on the modes of transmission, foci of origin, prevention, immunity and treatment. Though some doubt was cast upon the findings at the time, it has been only during our recent epidemic that definite denial of the specificity of the organism has been steadfastly maintained in many quarters. It required another pandemic, first, to determine the nature of the disease that we were dealing with, second, to prove its similarity to previous epidemics of influenza, and third, to furnish an abundance of clinical and pathological material to carry on further investigation.

There can be no doubt of the identity of the epidemics of 1889 and 1918. Both epidemiologically and clinically they are alike. The difficulty arises in attempting to place sporadic outbreaks and isolated cases of influenza under the same head. There is a strong tendency to classify several of the severe forms of idiopathic catarrhal fever and common types of acute bronchitis under influenza. In fact the names "Grippe" and "Influenza" have been so generally abused by both profession and laity as to constitute at least an annoyance in determining outbreaks of the true disease. This misnaming of minor ailments has probably resulted from attempts to put a blanket classification over some of the various infections of unknown origin. Too often the tendency exists among practitioners to magnify the importance of a simple rhinitis or pharyngitis. This is not a new practice. In James Jackson's "Letters to a Young Physician," he remarks: "When the great and learned have a severe bronchitis, there often is, among all concerned, a disposition to magnify the disease, and then call it influenza. Now, I could tell the reverend or the honorable gentleman, that when he has the influenza, the chance is that the domestics in his kitchen will have it too. I should not make this remark if I did not believe that the patient, who has his malady thus exalted by a great name, is often led into some unnecessary evils by the misnomer." Individual cases of influenza are not seen singly except under the rarest circumstances. Even minor outbreaks of acute rhinitis, and acute bronchitis seen frequently in large centers of population are unlike the true disease. The converse, however, is also true. When an epidemic is raging and the public mind is alert to the nature and dangers of influenza, many cases are reported as influenza that in reality are only mildly contagious nasopharyngeal or bronchial infections.

It is to be desired, therefore, that some ready means of identification of influenza be found. At present they do not exist. Clinical signs and symptoms will always be uncertain unless some differential point be discovered. If the specific germ be determined, that will be of real aid. Perhaps serum reactions will then be forthcoming. Levinthal, who worked with methods of culture of the bacillus of Pfeiffer, claims to have been able to agglutinate these organisms with patient and convalescent serum in dilutions one-fiftieth to one-four-hundredth. No confirmation of this work exists. (See further discussion under IMMUNITY and SEROLOGY). In this connection the question often arises concerning the cause of sudden outbreaks of pandemics. Weather, season, altitude and climate are known to exert definite influence at all seasons, in all climates, and in all varieties of atmospheric conditions. High or low barometric pressures, dryness of air, or precipitation of rain, mountain top or sea level, intense heat or frigid temperatures, none of these conditions in the least alters the course of the disease. In fact during the epidemic of 1918 influenza prevailed simultaneously under practically all these conditions.

One hestitates to consider telluric causes of epidemic outbreaks. The question is brought up at this point simply to state that a review of such observations on epidemics and pandemics gathered from every historical period are a jumbled mass of contradictory evidence that shed no light whatever upon the source of the disease.

No race is exempt from influenza. The disease is evidently more prevalent among Caucasians; endemics and pandemic recurrences are observed among these with great frequency. Other races, however. are equally and as severally affected. The North American Indian suffered frightfully during the last onslaught of the disease. Among the Eskimos the morbidity as well as mortality was very great. Both in Japan and China reports indicate that the disease was especially fatal. From October 1, 1918, to April 30, 1919, over 250,000 fatal cases of influenza occurred in Japan. Interesting datum from Tananarin, Madagascar, which has a population of 64,000, 98 per cent. of whom are natives, shows that 347 deaths occurred from influenza and pneumonia during the two weeks of the height of the influenza epidemic. Public health reports from the Union of South Africa in 1918 state that the total number of influenza cases which came to the attention of health authorities was 2,616,805, or nearly 43 per cent. of the population. This was considered a conservative figure, as the disease is not reportable. In the period from August to October, 1918, the total death rate from influenza was

22.8 per cent. Among the white population the rate per 100,000 was 826, whereas the colored population suffered a mortality to the extent of 2,719 per 100,000. Such reports would indicate that the black succumbs to the disease more readily than the white. The cause for this is probably not entirely racial. Hygenic conditions in general, medical care and personal attention account in part for it.

The age at which influenza most frequently appears is early adult life. However, it occurs at all ages. To arrive at reliable figures the method of house-to-house canvass after the epidemic period is past presents the only trustworthy way. General hospital statistics are not reliable because the age groups that are institutionalized during an epidemic are not proportionate. Nor are mortality rates a just means for this determination, because the deaths from bronchopneumonia and other complications vary at different age periods in life. During the recurrence of the disease in January and February of 1920, the Detroit Board of Health investigated every reported case of influenza. Its statistics are as follows: In a canvass following the epidemic of September and October, 1918, the data procured indicated that in 420 families where influenza prevailed there resided 2,012 individuals; of these 1,523 had influenza in some form, a morbidity of 75.7 per cent. in infected households. The following table illustrates the incidence rate as to age:

Age.	*No. of Cases.*	*Per Cent.*
Under 1 year of age	4	.26
1 to 10 years	27	1.78
10 to 20 years	201	13.19
20 to 30 years	691	45.36
30 to 40 years	344	22.58
40 to 50 years	151	9.92
50 to 60 years	86	5.65
Above 60 years	19	1.25

This incidence rate agrees fairly well with observations during the epidemic of 1889-90. However, the Public Health Reports issued in August, 1919, state that the case incidence was found to be uniformly highest in children from 5 to 14 years old and progressively lower in each higher age group. From the ages of 4 to 34 the rate of those suffering from influenza and pneumonia combined was over 300 per 1,000 persons. Several interesting deductions may be drawn. Under one year of age influenza is rare. Of the 4 cases recorded, 3 patients recovered and 1 died of bronchopneumonia. This was a nursing infant of two weeks, whose mother also had the disease and recovered. Up to the age of 10 the disease is relatively infrequent. From the tenth year on the percentage increases rapidly. The greatest morbidity is between the ages of 20 and 30. In all probability this would have been higher were it not that at this particular time many of those that would have been included in these figures were in military service. The disease is relatively rare after the age of 60.

Occupation has very little effect on the disease. The respiratory diseases are most prevalent in those whose vocations expose them to the trying conditions of bad weather. Influenza attacks those who live in protected places, such as inmates of prisons and asylums as well as those who live for the most part in the out-of-doors, such as farmers and laborers. The part that occupation plays has more to do with the resulting possibilities of contact infections. Thus the disease is diffused among factory employees, clerks, soldiers, institutional workers, who mingle freely with one another. Those on the other hand who work out of doors,as farmers, drivers, trainmen, are not as generally attacked. This does not apply to the severity of the disease. Strangely enough, as was repeatedly demonstrated during the epidemic in the Fall of 1918, the death rate of those in army camps coming from rural districts was far in excess of those who had spent their lives in crowded communities.

It has been generally supposed that the disease affected each sex equally. Statistics on this are variable. Of the 1,523 cases collected in the winter of 1918 in 400 families, 818 were females and 705 males. This may be explained on the assumption that a large proportion of the male population between the ages of 20 and 30 were in the army service. Statistics gathered during the wave of the disease in 1920 show a more equal division. Of 212 admitted to the author's medical service at Harper Hospital, Detroit, 118 were males and 94 females.

Bacteriology.—There is no general agreement at the present time as to the cause of the disease. The influenza bacillus as described by Pfeiffer in 1892 at the time of the discovery of this organism was generally accepted as the causative factor by contemporary bacteriologists and clinicians. Even up to the last pandemic little doubt was expressed in regard to the correctness of this view. However, at the present time considerable evidence is at hand questioning the assumption that holds the Pfeiffer bacillus to be the causative agent. Since the last great waves of the disease, the failure to substantiate universally the findings of the influenza organism has led to other points of view in regard to the etiology of the disease. Those who differ contend that the bacillus is just as prevalent in the secretions of the respiratory tract when an epidemic is not prevailing, that immunologic reactions are not convincing, that the disease has not been reproduced in animals or in human volunteer subjects, and finally that the organisms cannot be isolated in all or even in an approximately uniform percentage of cases. Though no other form of organism has been discovered that claims the right to be designated as the etiologic cause, many bacteriologists believe that the disease is produced by a filtrable virus. On one point general agreement seems to exist and that is that the chief respiratory complications of influenza, namely, the various forms of bronchopneumonia, may be produced by a variety of organisms, the nature of which varies greatly in different localities.

The Pfeiffer organism is a very small plump rod varying from 1 to 1.5 microns in length and from .4 to .6 microns in width. It is nonmotile. Its ends are rounded and it stains uniformly. Best results are obtainable with Loeffler's methylene-blue or with carbolic fuchsin diluted from 10 to 20 times. Gram's method will not stain the organism. MacCallum's method of staining in tissue yields excellent results. At times bipolar staining may occur, especially with dilute carbolic fuchsin. In old cultures branching as well as involution forms are observed. This tendency to pleomorphism has long been observed. Park, Coca and others have recently commented on it again. The bacillus is very sensitive to drying and to heat. Even on suitable media it dies out readily and requires frequent transplantation. It grows more satisfactorily on media containing hemoglobin. The ordinary method consists of pouring agar into Petri dishes and allowing it to solidify. Human, rabbit or pigeon blood is then spread over the surface of the plate. For inoculation the infectious material is rubbed up in sterile saline solution or bouillon and then streaked over the plate. This is incubated at 37° C. (98.6° F.). Control tubes of plain agar yield scarcely any growth of the Pfeiffer organism. A more satisfactory media is Avery's oleate-hemoglobin-agar which has the advantage of retarding the growth of strains of pneumococci and streptococci. The colonies are usually so small that it may require a magnifying lens to definitely reveal them. They develop in twenty-four hours, appearing as isolated colorless drops, lying often close together, but rarely coalescing. The colonies never change much in size or appearance except that the center may show a yellowish or brownish color. They may be overlooked because of the presence of staphylococci or other organisms among which they develop.

It is probably this difficulty in detection and isolation of the Pfeiffer organism that has in part given such a wide variation in results obtained during the last epidemics. Pfeiffer stated that the true organisms were found exclusively in endemic and epidemic influenza. His work was generally corroborated at the time. Apparently this opinion had prevailed until the epidemic in 1918, 1919 and 1920 gave the opportunity for additional confirmation and more critical investigation of the subject. This has left the matter entirely in doubt. So widely are conclusions at variance on the point of etiology that the question is scarcely a controversial one at this time. Neither extreme seems to have any patience with the convictions of the other. It will require at least another epidemic to reach a solution of the matter.

The report of the British Commission to investigate the influenza epidemic in the armies in France published the following table:

Material Examined.	*Number of Attempts.*	*Number of That Bacilli Influenzæ Were Recovered.*
Sputa	222	91
Nasopharyngeal Mucus	164	60
Blood	68	2

In this report the experience of the members of the Commission seems to point to the fact that earlier attempts to recover the organism were unsuccessful, whereas later the bacillus was found in from 80 to 100 per cent. of the cases. They say: "When tracheitis, bronchitis or bronchopneumonia existed, *bacillus influenzæ* was generally recovered with ease. They often occurred in great numbers and cultivation of sputum from these cases afforded nearly pure cultures of *bacillus influenzæ.*" Hence this Commission considers that the evidence for the Pfeiffer bacillus being the etiologic cause of influenza is the frequency of the organism in the respiratory tract of afflicted subjects, the recovery of the organism from the blood in a few cases, its presence in lesions at autopsy and some immunologic observations made in a few instances.

MacNeal in a "Report on Influenza in the American Expeditionary Forces" believes the Pfeiffer organism to be the "apparent cause" of the epidemic, but states that "causal relationship" has in no way been proven. It is quite evident that the same variability in findings existed in the laboratories of the American Expeditionary Forces as elsewhere. The demonstration of the *bacillus influenzæ* varied from a few per cent. in some reports to 100 per cent. in hospitals where cases were "properly examined."

Japanese investigators corroborated the work of Pfeiffer. They have found the *bacillus influenzæ* in a large majority of their cases. Though they do not regard the large incidence of the bacillus as proof of the etiology, its high incidence in infected patients during epidemics lends weight to the assumption.

A tremendous amount of data has accrued from work in the various army camps. The reports are widely at variance. In all of the camps the influenza bacillus was recovered from the blood only in rare instances. At postmortem the percentage of recovery was somewhat higher. It is also to be noted that at many camps the percentage of positive cultures of the Pfeiffer bacillus increased with the progress of the epidemic, so that at the height of the epidemic the largest relative number of positive influenza cultures were obtained. Opie and his coworkers in one camp found the influenza bacillus present in the sputum of 35 per cent. of healthy soldiers chosen at random. On the other hand, he found approximately the same percentage of positive cultures in the sputa of a large group of soldiers suffering from measles. MacCallum working in two different camps found the Pfeiffer organism in every case examined at Camp Dix and present only in rare instances in the patients at Camp Lee. This same variation in statistics that was found in army hospitals obtains as well in civilian institutions. Studies made among large civil populations show a larger percentage of recovery of the Pfeiffer organism than in army camps. Jordan found influenza bacillus in 64 per cent. of cases examined in Chicago. Park and Williams during the first epidemic of influenza report it to be the predominating organism.

There seems to be a considerable difference of opinion as to what part of the respiratory tract is the best source for finding the influenza bacillus. The sputum, saliva, nasal secretions, pharyngeal and tonsillar swabs may yield a different percentage of positives than a large group of cases. However, the tonsils and the nasopharynx seem to be the most likely place from which the organisms may be obtained on culture. In the light of this and especially owing to the fact that a uniform technic is not generally observed the percentage of recovery of the organisms may vary widely.

A large amount of work has been done on the various strains of influenza bacilli. Bacteriologists prefer to speak of the Pfeiffer group. Some strains of the organisms will grow only in the presence of hemoglobin. Certain strains produce nitrates; some produce indol; others fail to do so. Though cross agglutination between different strains may occur, it frequently happens that individual types of the Pfeiffer bacillus will be agglutinated only by the serum of the patient from whom the organism is recovered. It has been suggested that an organism presenting tendencies to such marked pleomorphism is virulent only at certain stages in its development. The theory has been advanced also that certain strains become virulent depending upon the condition of the host.

It has been suggested particularly by French and English observers that a filtrable virus is the inciting agent. Certain experiments have been adduced in support of this view. Bradford and his coworkers have described cocci which are supposed to produce injury in the respiratory tract, making it possible for secondary invaders to produce lesions typical of the bronchopneumonia as seen in influenza. This work has been accomplished in animals. That the theory of a filtrable virus is possible cannot be discarded. A primary damage to the respiratory tract by an unknown poison or organism may occur, preparing the soil for the secondary invaders. This is similar, as has been pointed out, to that which occurs in the bronchopneumonia, complicating measles (Wolbach), bubonic plague (Symmers), and following inhalation of lethal gases (Winternitz).

These facts lend weight to the denial of the influenza bacillus as the true inciting agent. They are further supported by the failure of the organism of Pfeiffer to produce the disease in lower animals, much less in man. Rosenau, Keegan, Goldberger, Lake and Leake have attempted in volunteer subjects to reproduce influenza by injecting into healthy subjects infected material taken from the secretions of known sufferers of influenza. Though in a few instances a mild form of respiratory disease was produced, typical cases of influenza with pulmonary complications did not result. Blake and Cecil have recently succeeded in producing influenza in monkeys by the instillation of cultures of influenza bacillus into the trachea. Yet the respiratory symptoms thus produced are not much different than might result from the instillation of any fresh bacterial flora into a mucous membrane previously uninfected by such an organism. Olitsky and Gates, after passing infected material through a Berkfield filter, were able to infect rabbits and produce symptoms typical of the disease. Their conclusions after a long series of observations are, that a filtrable virus is a primary invader and that the bacillus of Pfeiffer may be one of the secondary organisms producing other features of the disease.

In light of all these facts, it would seem that bacteriologic evidence has not yet demonstrated conclusively the etiology of influenza. In truth one is forced to admit that the bacillus of Pfeiffer may or may not be present during an epidemic, but may act as a secondary invader and produce unmistakable complicating features in the course of the disease.

MODES OF TRANSMISSION.—With the act of coughing and sneezing droplets of infected secretion are sprayed in all directions. This is probably laden with highly infectious virus that readily spreads the disease. During the epidemic of 1918-1920 masks were generally worn in hospitals, camps and even in public to act as filters against infection. Unguarded coughing, sneezing and expectoration are without doubt the most prolific sources of dissemination of infectious material and the most frequent cause of direct contagion. (The efficiency of masks will be discussed under prevention of influenza.)

Food stuffs and drinking water are also a very probable source of spreading contagion. In kitchens and messes where large quantities are handled this may readily occur. Cooks and food handlers can very quickly disseminate infection. Food stuffs in cafés and restaurants that are exposed form a ready medium for the collection of organisms. Whether the specific germs of influenza live any appreciable period of time in such exposed places has not been established.

Utensils, dishes, cups, etc., form a convenient harbor for infected material. This is true where large numbers deposit their soiled dishes into common vats for purposes of washing. Especially strong is the possibility of transmission of infection in this manner where care has not been taken to use boiling water in the process. Cummings believes that this is one of the most likely ways in which an infectious agent may be widely diffused. In camp messes and in large kitchens where vats are utilized and where scrupulous care is not always employed, broadcast infection may speedily result.

It would appear doubtful that merchandise, books, or linens could retain the infectious agent, and transmit it to others. Assuming the Pfeiffer organism to be the true cause, its viability much less than its ability to survive in such media is highly improbable. It is quite unlikely that the influenza virus would remain active.

IMMUNITY.—The immunity conferred by an attack of influenza is relative. Individuals have been known to have several attacks during their lifetime. Such may be classed as susceptibles. One explanation for the cause of pandemics recurring about every two or three decades, is that in this period a new generation of susceptibles has grown up in whom the disease finds fertile soil for its quick propagation. However, all who have been previously free from influenza, do not acquire the disease during a pandemic. This leaves others to develop it in recurring epidemics. When one considers that during the recent pandemic the majority afflicted were under the age of 40, one can conclude that the small morbidity over that age was due to an immunity acquired in part during or since the pandemic of 1889-1890. Undoubtedly those who have survived attacks of the disease in 1918, 1919 and 1920, will be relatively immune in the future. To what extent the uninfected population in various parts of the country will be attacked by the disease in succeeding waves of influenza cannot be estimated. As the percentage of the population attacked varied from 15 to 53 per cent., the likelihood is that the incidence in the future epidemics will be in inverse ratio to the previous ones.

A general survey shows that individuals who have suffered from influenza rarely have a second attack. In Baltimore where the first canvass of 33,776 people was made between November 20 and December 11, 1918, a second canvass of the same population was made in January to determine the extent of the recrudescence reported in December. Among 32,600 people included in this second canvass, 724 cases of influenza were found to have occurred since the previous survey. Of this number, 121 cases were reported as second attacks, but on investigation through the attending physicians or by a medical officer, the clinical diagnosis of both attacks as influenza was confirmed in only 26 cases, or 0.37 per cent. of the total. Even in these cases the diagnosis is necessarily uncertain. Considering that 23 per cent. of the population had had influenza prior to December 11, the proportion of second attacks should have been much greater if no immunity had been acquired. Though no race or class is immune, infants, as has been stated elsewhere, rarely acquire the disease. There is perhaps also a natural or congenital immunity as is found in other acute infectious diseases. Physicians and nurses are probably not more exempt from influenza than others. In regard to physicians, the only available data is that from the army. Among the medical officers in cantonments the rate was usually proportionate to that of the line officers. During the first wave of the disease in September and October of 1918, in a large general hospital in Detroit, 51 nurses were stricken. At the time there were 178 pupil nurses of ages ranging from 19 to 31 enrolled in the school. This is about 40 per cent., a figure which corresponds with the general incidence elsewhere. Practically no reliable work has been done on the subject of acquired immunity. Though many have worked with the influenza bacillus in an endeavor to establish such an immunity, nothing of value has developed; nor can definite results be hoped for until the validity of Pfeiffer's bacillus or some other organism as the causative agent be proven.

On the assumption that the influenza bacillus is the etiologic germ, preventative inoculation was freely practiced during recent epidemics. Though some definite claims have been made, the results are so widely at variance and the corroboration of carefully conducted work is so difficult as to make observations quite valueless. In short, the diversity of factors that enter into an epidemic, the variability of incidence, the unreliability of definite diagnosis in general, and the brief course of an epidemic, make positive statements with reference to the establishment of immunity quite impossible. One cannot gainsay or discourage the enthusiastic claims of honorable practitioners who believe they have rendered their patients real service by preventative inoculations. At the same time, such experiences must not be confounded with controlled experiments and observation, which unfortunately up to the present do not exist. (These statements in no way apply to preventative inoculation with reference to strains of pneumococci and streptococci found complicating cases of influenzal bronchopneumonia.)

Prevention and Contagion.—Many months before the last pandemic had reached the Western Hemisphere, physicians and sanitarians were discussing means of prevention of spread of the disease on this continent. History had shown that the disease spreads definitely along lines of human travel and that its rate was dependent upon the speed with which this took place. The opportunities at this time were splendid. Ocean travel except for troop ships, convoys, naval vessels, and supply ships was restricted. Ships sailed only under most stringent regulations. The medical personnel at ports on the Atlantic Seaboard strictly scrutinized each ship. Though the disease was prevalent in the European armies in epidemic form in April and May, 1918, it did not reach these shores until August. Several instances of influenza on shipboard were reported that summer. The disease probably made its first appearance in Boston, though it was soon reported from New York, Philadelphia and Baltimore. Thereafter it was spread rapidly through the United States. Hence it becomes at once evident, that in spite of strict surveillance, under unusual conditions, general sanitary measures did not suffice to prevent its spread.

The statement has been made on the strength of casual observation that the period of greatest contagion is during incubation; that after the disease is fully developed transmission does not so readily occur. Bloomfield and Harrop cite certain observations to substantiate this. Rosenau was unable to inoculate volunteer subjects with disease from patients definitely ill with influenza. Blake and Cecil, on the other hand, have been able to infect healthy individuals, and reproduce the disease from the infective material of influenza patients.

On the assumption that mouth and nasal secretions were the most prolific sources of contagion, masks were worn in many quarters. Much work was done to determine the size of mesh and number of plies of gauze necessary to prevent the expulsion of sputum particles through the mesh. The purpose of the mask was also to guard against the infected spray of those who sneezed or coughed. How useful the mask was is doubtful. In the hands of physicians and nurses who are careful in its adjustment and in the frequency of sterilization, it must have a relative value. In the hands of the untrained, however, it is useless if not a positive menace. During the epidemic of 1918 health officials in some communities advised the wearing of the mask. Naturally a fantastic assortment of such protectors came quickly into use. Some masks covered the nostrils, and many were crumpled carelessly in the pocket to be worn occasionally; frequently such protectors had collected enough dirt to beggar description.

Two conclusions can be drawn: (1) In the hands of those who recognize their use and purpose, the properly made gauze masks afford some protection.

(2) When properly adjusted to the influenza patient and frequently changed and sterilized, the gauze will in a degree prevent spread of contagion.

Great care should be exercised in the handling of infected material. Cooking and eating utensils, linen, wash water and basins are very likely to be common carriers of influenza. How long the virus is viable under such conditions is unknown. Ample evidence exists, however, to make it imperative to use every precautionary measure to prevent diffusion of the infection by such means. In this connection may be mentioned a much neglected yet highly essential measure that will prevent spread of contagion. Careful washing of the hands with good soap and the scrubbing and cleansing of the nails should be religiously practiced. It seems somewhat superfluous to mention a procedure that is a universal custom; yet its very simplicity makes it a too often neglected practice among busy nurses and physicians.

The segregation of patients suffering from influenza by means of screens, or cubicles is always to be desired. Where carefully carried out along with other preventive measures, it definitely isolates an infected patient from the remainder of a ward. How long such isolation should be maintained depends upon the individual case. It should never be less than a week.

Much difference of opinion exists as to the real virtue of quarantine. During an epidemic the isolation of a dwelling by placard should be strictly maintained. It would seem reasonable, however, to allow the noninfected to go and come at will. During the epidemics of 1918 and 1920 diligent investigations were made, when instances of "carrying the disease" (a healthy individual transmitting influenza from an infected household to an uninfected one) were reported. Not a single case could be proven.

In general the promiscuous congregation of people in theaters, churches, schools, and halls of all descriptions should be prohibited. The plea against such measures, especially in manufacturing centers, is that it would be better to permit quiet assemblage in well-ventilated meeting places, and thereby prevent collection of small groups in the stuffy quarters of a workman's house. Furthermore the enlivening influence of other surroundings may have a refreshing effect upon the wearied psyche of the toiler. Whatever the fundamentals of such arguments may be, no attempt to analyses can be made in this article. It would seem that for the greatest good to the greatest number, when an epidemic is at hand, all unnecessary intercourse, crowding, and intermingling under any and all circumstances should be prohibited. It should be maintained until the epidemic is past. Probably sunlight and fresh air are the greatest boon. Large and spacious parks and playgrounds, well-lighted and well-ventilated schoolrooms, sunny and airy restrooms, clean and roomy public conveyances, all these in a measure are preventive measures that resist the spread of influenza.

Symptomatology and Diagnosis.—INCUBATION PERIOD.—It is generally agreed that the incubation period of influenza is very brief. From an epidemological standpoint this is at once apparent. The almost simultaneous appearance of the disease in large areas suggests this. The older writers were impressed with this suddenness of outbreak and speed of diffusion, and therefore spoke of it as a "visitation of God," or a "bad wind" or a "blast of the stars." It was ascribed to the effect of earthquakes, which by vast disturbances of soil liberated a miasm capable of being transported to great distances by atmospheric currents.

There is much evidence at hand to prove that the disease can be quickly spread. Probably the first reliable work on the subject is the Report of the Commission of the Clinical Society of London *(Longman, Green & Co., London, 1892)* to investigate the incubation period of certain infectious diseases. They found it to range from several hours to four or five days. During this last pandamic opportunities for determining this were numerous. At the Naval Training Station at River Rouge, near Detroit, Michigan, a number of sailors were received from Boston late on Saturday afternoon. Influenza had appeared at the Boston Station prior to their departure. They were assigned to a particular barrack. On Sunday morning 2 of the men reported at sick call. The following Monday morning 18 cases developed among the men in the barrack occupied by them. Thirty-six hours later influenza had spread throughout the Station. Influenza had not made its appearance in Detroit or vicinity at the time.' Though this incident does not establish the time of incubation in those arriving from Boston, it places the period of development of the disease in the River Rouge cadets between Saturday at 4 p. m. and Monday at 9 a. m., a maximum of forty hours. All were typical examples of influenza. At that time 4 patients, one of whom was a Boston recruit, had developed complications of bronchopneumonia.

The various reports from the English army are inclined to place the incubation period at from two to four days. Continental observers, however, believe it to be shorter. The Germans consider it to be between one and three days. French and Italian writers state that it may develop in twelve hours after exposure. A few still cling to and offer evidence to prove that influenza may develop almost spontaneously; at least that the rapidity of its diffusion and the suddenness of its attack speak for a very short period of incubation. Both the general and theoretical knowledge of immunity and infection render this idea untenable.

Without having definitely settled upon the specific causative virus, or determined the mode of transmission, we must for the present accept twenty-four hours as the minimum incubation period. It is doubtful if influenza ever develops in a shorter time.

MODE OF ONSET.—The onset of influenza is sudden and violent in the great majority of cases. In a small proportion it is gradual, reaching its acme within twelve hours. It is somewhat misleading to divide the disease into respiratory, nervous, gastro-intestinal, circulatory and other forms. Though onset symptoms may predominate in one or another system, they have after all so much in common as to make such classifications superfluous.

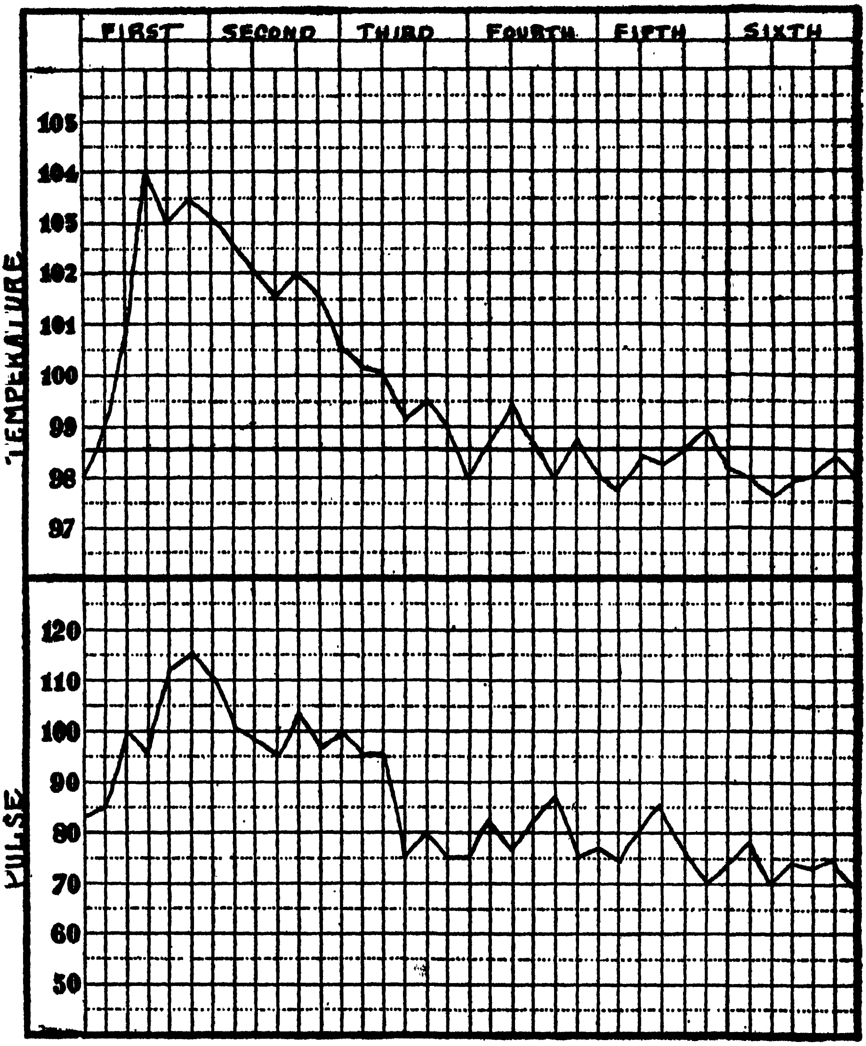

CHART I

When the disease sets in abruptly, there is sudden chilliness, fever, headache, pain in the back and legs, and a sensation of intense prostration. Later, respiratory, gastro-intestinal, nervous, circulatory and other signs develop. There is probably no disease in which the initial syptoms are more violent. Victims are literally stricken down in their tracks. Individuals at work are suddenly and utterly overcome, or they are awakened from a sound sleep with a feeling of complete prostration.

Chilliness is usually present. This may vary from a "creepy cold" feeling to an intense rigor lasting fully an hour. At the same time the fever rises. It may vary from 100° to 105° F. (37.8° to 40.6° C.). Some-

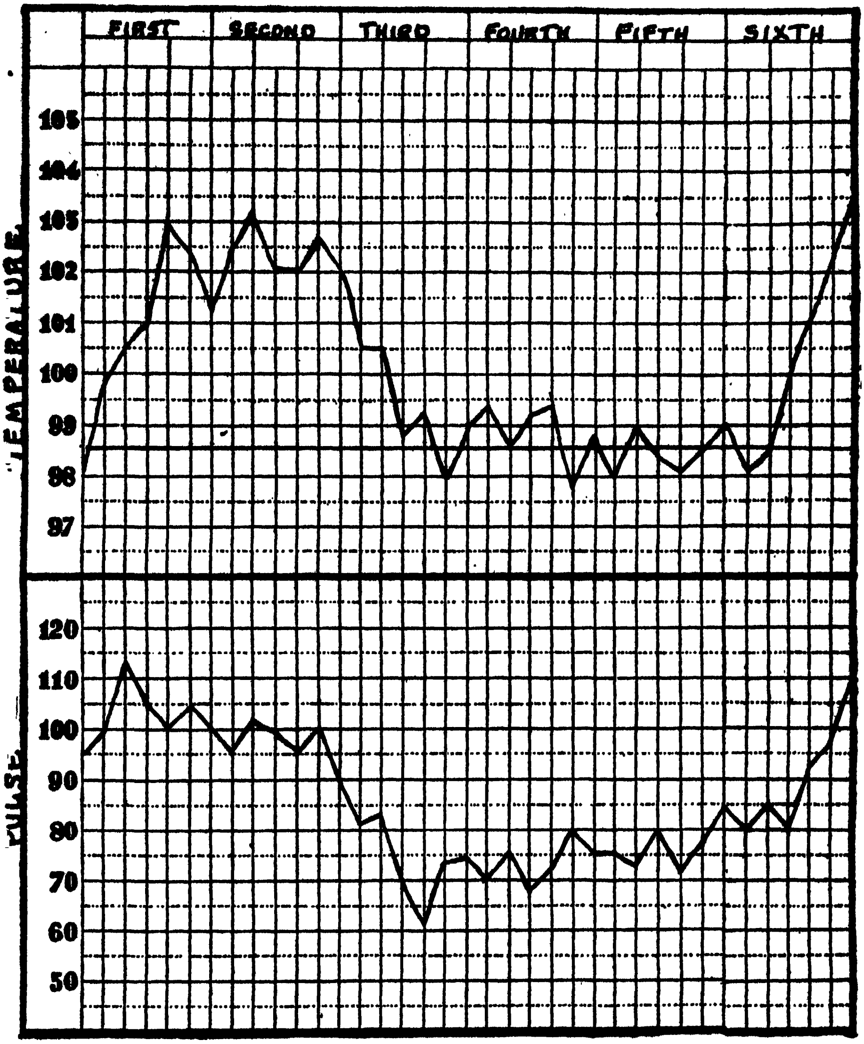

CHART II

times the initial rise is the highest point it attains during the course of the illness. Less often the temperature gradually rises to reach its maximum on the second or third day. There is nothing constant about the fever curve. In mild cases the febrile reaction may be completed within forty-eight hours, the intense rise being followed by a somewhat rapid fall (*See* CHART I). Even in severer cases this sometimes occurs the other symptoms following later, or the secondary rise of temperatrue due to complications coming after a three-day febrile interval (*See* CHART II). Such cases have a rapid lysis. Usually after the initial high point has been reached, the fever descends gradually so that in the

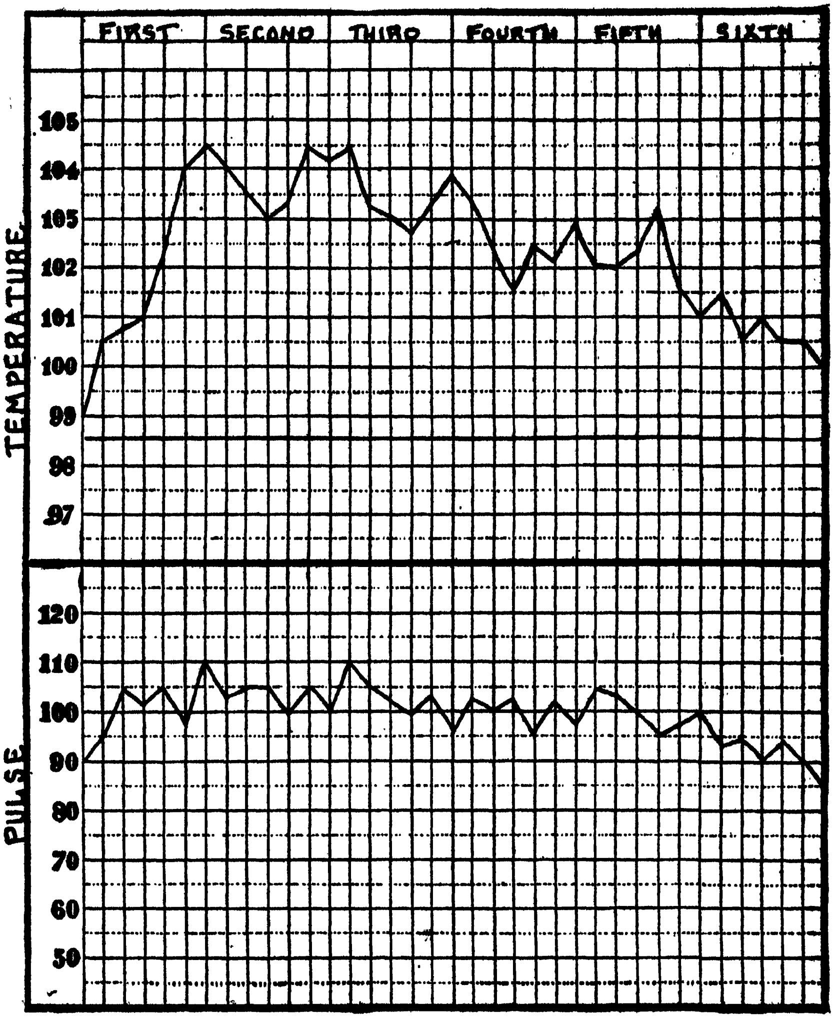

CHART III

course of several days it reaches normal again (*See* CHART III). This pyrexial period lasts from four to eight days, the temperature range being between 101° and 103° F. (37.8° and 39.4° C.).

Headache is among the most common and severe symptoms. During the epidemics of 1918 and 1920, in private, in hospital and in military practice, it was present in over 80 per cent. of the patients. It is chiefly characterized by its intensity and violence. The pain is almost always frontal and referred chiefly to the orbits, occasionally to the region of the frontal sinuses. When the pain is occipital, it is associated with

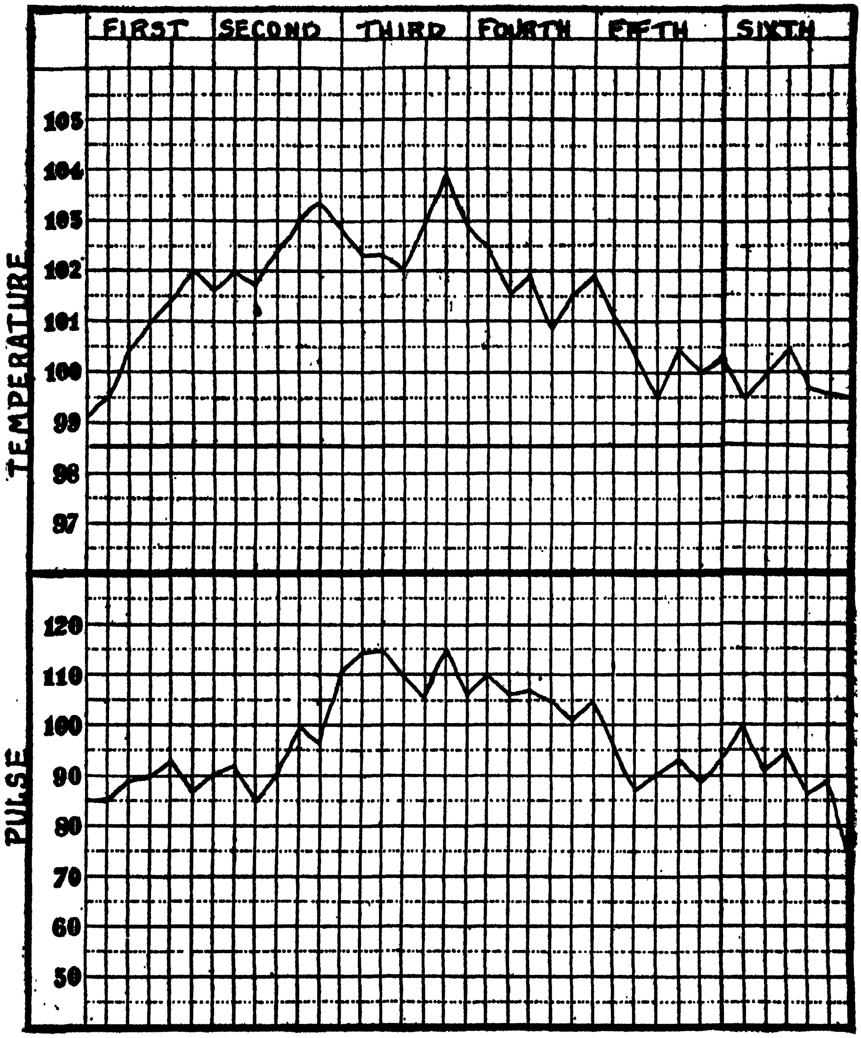

CHART IV

the pain in the back. It is then not as intense and as a rule lasts somewhat longer.

Pain in the back is very common. In some instances it is so severe as to simulate dengue. It is present in about one-half of all cases. Located chiefly in the lumbar region, it radiated into the hips and down the thighs. Soreness of the joints and muscles about them is frequently complained of. They are stiff and painful, but never swollen or reddened.

Course With Gradual Onset.—When influenza develops gradually, the earliest symptom is a feeling of weakness or malaise. Patients usually complain of a cold, of nausea, or of a sense of prostration. Apathy and mental torpor are present. The fever gradually rises, often reaching 104° or 105° F. (40° or 40.6° C.) at the end of seventy-two hours (*See* CHART IV). Such patients are not always chilly, but complain more of a sense of heat and suffocation. Headache is not usually so intense though generally present especially with the increasing pyrexia. Back and leg pains are less frequent. The course of the temperature is variable, lasting from four to ten days. When the fever runs a longer course, the attack is usually complicated by some severe secondary infection. The pulse rate is accelerated. Its rise, however, is not proportionate to the temperature, except when severe complications supervene. At such times the rate increases, indicating more definitely the severity of the secondary infectious invasion. Occasionally a tachycardia develops during convalescence. Bradycardia is extremely rare. The author observed it but three times in a large series of cases during the recent epidemics. The respiration is usually accelerated in proportion to the temperature. In the presence of a complicating pneumonia the dyspnea that takes place is due to the acute pulmonary condition.

Among the early symptoms is a catarrhal inflammation of the entire upper respiratory passages. This is apparent in fully 90 per cent. of the cases. The eyes are painful; lacrimation accompanies the conjunctivitis; photophobia is marked; sneezing and coryza may occur; rawness of throat with cough and substernal tenderness give evidence of an early pharyngitis and tracheobronchitis. As the disease progresses the infection remains either stationary or spreads into the eustachian tubes and sinuses, or bronchi and lungs, as the case may be. When the attack of influenza runs a favorable course without developing further respiratory complications, symptoms quickly subside; or the serous secretion of the first two days becomes thicker and assumes a purulent character, frequently with admixture of blood from the nasal passages. The bronchitis is generally mucopurulent and remains so until the inflammation has completey subsided. The sputum is thick and grayish with slight yellow tinge at times.

Gastro-intestinal complaints are present at some time during the course of an attack of influenza. The earliest symptom in a small percentage of cases is vomiting. This generally accompanies the prostration and intensifies it. Loss of appetite comes early, however. Occasionally vomiting does not appear till the third or fourth day. It is then a feature of the anorexia. It is a most troublesome and distressing symptom at any period of the attack. Even the attempt to take water will bring on violent nausea, and thereby add markedly to the discomfiture of the patient. It gradually subsides, but may recur again with elevation of temperature or other sequelae. In occasional cases the sense of taste and smell is lost. These symptoms are never persistent.

Symptoms from the intestinal tract are purely functional in character. They vary greatly. Some observers have made little or no mention of them, considering no doubt that they were such as might occur in the course of any other acute infectious disease. They are worthy of note only when they are unusual in character or degree, or occur in so striking a series of cases as to be out of the ordinary. During the epidemic wave of 1920, diarrhea was a troublesome symptom in quite a number of cases. Occasionally it was accompanied by blood. The stools were mixed with stringy mucus which persisted long after the general symptoms had subsided. This is the only evidence that influenza at times develops definite signs of a catarrhal, inflammatory or ulcerative condition. Tenesmus is rarely encountered. It occurs more frequently in children. Abdominal pain of griping character is associated with the diarrhea in some cases. Constipation is no less frequent in influenza than in other acute infections. It is rarely obstinate, except when alternating with diarrhea. Under these conditions it is alarming, the bowel apparently assuming a paralytic condition. With this ileus, tenderness and meteorism develop sometimes to a marked degree.

In a few cases influenza has been ushered in with sharp abdominal pain. Such attacks have simulated *acute appendicitis.* In fact localizing signs have been such as to warrant occasionally a suspicion of an inflammatory condition in the right iliac fossa. Leichtenstein quite positively refers to cases that he observed during the epidemic of 1889 in which symptoms referable to the appendix occured coincident with an influenzal infection. Such cases were seen during the past pandemic. Owing to the great readiness with which surgery is sometimes resorted to, especially in suspicious conditions in the cecal region, a few normal appendices were removed. Such patients ran their influenzal course afterwards. In the unoperated case the symptoms about the cecum gradually subside with the supervention of generalized influenzal infection. This statement in no sense intends to minimize the importance of bearing in mind the dangers of an acute appendicitis preceding or occurring coincidently with influenza. Two cases of acute gangrenous appendicitis were brought to Harper Hospital within twelve hours of each other during the epidemic in 1920. Both after appendectomy continued with grippal symptoms, developed bronchopneumonia and recovered.

Jaundice is a variable symptom. Earlier writers refer to it as of occasional occurrence. In some localities it appeared more frequently than in others. During the past pandemic very few of the English and French observers described it. (In some of the American army camps it was reported in as high as 8 per cent. of those afflicted. This figure however, also includes those developing jaundice during the complicating bronchopneumonia.) Jaundice is a rare symptom during the early stage of influenza. It is seldom evidenced by more than a mild tingling of the sclera and slightly darker urine. Acholic stools are not seen. The liver scarcely enlarges, though the margin is sometimes tender. It is probably a mild cholangitis which lasts but a few days, and clears up promptly and completely with the subsidence of other symptoms.

Symptoms referable to the nervous system are among the common manifestations. They vary with the epidemic as well as with the locality, race, and age group affected, and may be psychic, cerebral or somatic in character. The mental states are seen in all grades, from mild torpor to profound depression; or they may range from light delirium to extreme mania. In all cases they are of toxic infectious origin. Most patients who present any degree of torpor have a tendency to listlessness and apathy. They frequently, when undisturbed by pain, sleep from twelve to twenty-four hours. During the pronounced depression they become unresponsive, refuse to eat and resist treatment. Mild delirium often accompanies hyperpyrexia, at times with slight aberration, disorientation or hypomania. Sleeplessness is a troublesome condition at these times. When excitement is more pronounced, the patient is markedly restless, and jactitation, twitchings and even extreme frenzy requiring restraint are seen. These symptoms usually subside in the majority of cases in a short time. In a few instances, they are prolonged and extend well into the convalescent period before they ameliorate. Postinfluenzal psychoses are described under COMPLICATIONS.

In addition to the headache and backache so frequently seen, neuritic pains are often of a troublesome nature. During the height of the disease they are persistent in character, radiating into the extremities and disturbing sleep. They are often so severe that the patient cannot touch, much less lie, on the affected part. Pain persists sometimes for many weeks. In prolonged cases the pain is localized usually in one extremity. It is sharp and continuous in character, frequently disturbing rest and interfering with use of the affected part. Polyneuritis is not so frequently observed. It is usually less severe, but may render the patient helpless. The tenderness along the nerves is accompanied with a general hyperesthesia. Though a motor neuritis with or without the sensory affection has been described, it is far less common. Individual paralyses, loss of reflexes, and group muscle palsies have been reported. These motor symptoms were not observed during the 1918 and 1920 epidemic except as manifestations of an encephalitis lethargica. This condition will be described under COMPLICATIONS.

The course of the disease is variable. Early in an epidemic the cases are milder. By the time the disease is well established severe forms develop. The shortest duration is about three days during which the symptoms of invasion, the febrile reaction, the defervescence and the convalescence follow in quick succession. Such patients sometimes present a very important problem in management. After two days of general well-being without rise of temperature, the subjects consider themselves too well for further restraint, get up and are about. It is not infrequent for a secondary rise of temperature to take place at the end of forty-eight hours and even seventy-two hours, usually ushering in a bronchopneumonia. The course is then characteristic of the complicating lung infection.

The duration of the average case of influenza is from eight to ten days. The convalescence may be much protracted depending upon the previous condition of the patient and the severity of the attack. Uncomplicated cases rarely last over two weeks. In such patients the onset is usually gradual, the febrile period exhibits irregular fluctuations and the decline of the disease is marked by slight irregular remissions before complete convalescence begins. Relapses are quite uncommon. Recurrences of fever are generally due to complications. Without definite diagnostic criteria, one cannot be sure whether the secondary return of symptoms described previously is due to a relapse of the disease or to the presence of some intercurrent infection. Relapses should at all times be regarded with alarm, and strict measures be taken for the care of the patients.

Physical Examination.—There is something quite striking and characteristic about the appearance of a typical case of influenza. The patient looks prostrated. The face is suffused and red, almost cyanotic in color. The eyes are red and swollen due to the injection and inflammation of the conjunctivæ. The lips are red and thick. In fact the same duskiness of the skin may be spread over the neck and chest, at times extending over the trunk and extremities. The eyes are held closed in most instances, due to the orbital pain and photophobia. The duskiness of the skin is sometimes the only feature. As such it may be quite persistent. When it extends over certain portions of the body, it gives the appearance of a blotchy erythema. A rash may be present. This is not characteristic of any special form of skin lesion, nor does it maintain a resemblance to any form of the acute exanthematous fevers. In a few instances an urticarial eruption has been observed with quite persistent itching. No large wheals are seen. In a few instances a morbilliform rash on the arms, shoulders and legs has been described, lasting about twenty-four hours. A desquamation of fine brawny character has occasionally followed. Sudamina in severe cases frequently occur. There is nothing characteristic about their appearance or presence. Herpes labialis may develop in uncomplicated cases. They are very troublesome and often quite extensive. They occur more frequently when pulmonary complications supervene.

The tongue presents nothing that can be called characteristic. In the beginning it is heavily furred, thick, red and dry. Later on as it becomes moister, the edges and tip clear, and appear deep red, whereas the surface has a thick grayish covering. The mucous membranes are deeply injected. There is frequently a sligh fetor, though with nothing suggestive of the disease about it. The fauces are generally fiery red, remaining so throughout the first few days. Then they take on an injected appearance, the fine capillaries often being apparent. The pharnyx is glistening and dry, except when covered by grayish yellow mucus or mottled by the appearance of swollen lymphoid nodules. Throughout the disease and even into convalescence the inflamed pharynx persists when other signs have vanished.

Cervical adenitis is rare. Glands that have been palpable before the onset of the influenza do not increase in size. Only in instances where ear, tonsillar and other complications occur does an adenopathy become manifest. Examination of the larynx and upper part of the trachea by laryngoscopy shows an extension of the inflammation observed in examination of the fauces. In uncomplicated cases examination of the lungs and bronchi reveals nothing. Therefore it should be regarded with suspicion as indicating an oncoming bronchitis or pneumonia whenever râles of any description are audible during the acute stage of influenza.

There are no changes in the heart outline either by percussion or fluoroscopy. The pulse is rapid, varying from 110 to 120 at the onset, but in the average case subsiding quickly with the fall in temperature. As a rule, the pulse is soft and quick, and the volume small. In mild cases the pressure as in all acute febrile states falls slightly. In the severe types, marked vasomotor syncope is seen. The systolic pressure may fall as low as 75 and the diastolic to 50. While a fair pulse pressure is maintained in this manner, the picture presented in such severe states resembles, with the vomiting and frightful prostration, all the features of syncope in Addison's disease. Vasomotor changes in these instances are striking; mottling of the skin occurs with alternate flushing and pallor; in rare instances a *liene blanche* has been observed. Heart sounds maintain their normal quality. As the disease progresses the rate gradually subsides with the fall in temperature. Only in cases with pneumonic complications does the rate remain rapid, ranging from 110 to 130. This is not of serious prognostic omen despite the fact that a persistently rapid pulse in acute lobar pneumonia has a grave significance.

Abdominal examinations reveals nothing abnormal. The liver is not felt. There is no meteorism. Epigastric tenderness occurs occasionally in cases associated with gastro-intestinal symptoms. In a small number of cases the spleen is palpable. This recedes with the subsidence of the acute symptoms of the influenza.

Bleeding from the mucous membrane is fairly frequent. In a few instances bleeding from the gums has occurred. Hemorrhoids often bleed, especially when bowel disturbance occurs. Menorrhagia has been noted in many instances, especially when the invasion of the disease occurs during the menstrual period. Epistaxis is very common. With the onset of influenza the congested condition of the nares predisposes to hemorrhage. Excessive bleeding frequently takes place, so that patients are at times quite exsanguinated. Repeated hemorrhages occurring throughout the course of the disease are likely to become a dangerous element in individual cases. In rare instances hemoptysis has been reported during influenza. Though it is not an uncommon symptom when bronchopneumonia has developed, its occurrence otherwise is quite doubtful.

Laboratory Findings.—The urine possesses the usual characteristic of any febrile state. The quantity is somewhat diminished. The specific gravity is increased. The color is darker, usually a yellowish brown. The reaction remains acid. A trace of albumin is occasionally present. Glucose is absent. Ketone bodies are not found except small quantities of acetone at times after the patient has been without food. Microscopically a few renal cells with an occasional granular or cellular cast may be found.

The spinal fluid is uniformly normal. The pressure is not increased, the cell count is not elevated, nor are there any changes in the globulin, Fehling's, Nesslerization or colloidal gold curve reactions.

The red cell count remains normal. The same is true of the hemoglobin content. The leukocytes in most instances are definitely affected. During the first forty-eight hours after onset the total count may either remain constant, or a definite leukopenia may be found. In an uncomplicated case the count may go as low as 1,200 white corpuscles per cubic millimeter. This may persist for many days, gradually returning to normal with convalescence. Less often a leukocytosis is present from the outstart. Though signs and symptoms of a complication may be lacking, there is strong argument for the assumption that a secondary infection is always present, producing the elevation of the white cell count. The differential count at all times shows proportionate changes in the polymorphonuclear cells depending upon the degree of leukopenia or leukocytosis. It is a striking fact that in a good many cases of bronchopneumonia following influenza a persistent leukopenia prevails during the course of the disease. There is as a rule, however, an antemortem leukocytosis in all such cases.

The oxygen containing power of the blood is normal in influenza. With the complication of bronchopneumonia this oxygen content or amount of oxygen unsaturation of the venous blood does not vary from normal except as the cases approach a fatal termination when the values fall. In other words, the capacity of the red blood-cells for carrying oxygen in no way varies with fluctuation in temperature, pulse, respiration or intensity of the disease process. The anoxemia as evidenced by the cyanosis in many cases is probably due to the exudation that occurs in the alveolar spaces, preventing the inspired air from reaching the endothelium of the vesicles.

CONVALESCENCE.—Convalescence is variable, depending upon the previous condition of the patient as well as the severity of the attack. In mild seizures the recovery is prompt and complete. However the more protracted cases are followed by slower convalescence and by an order of symptoms quite characteristic of the disease. Weakness, anorexia and prostration may persist for weeks. Usually there are not definite somatic symptoms. Drenching sweats any time of day or night may occur. Profound asthenia persists sufficient to confine the patient in bed long after the usual expected period for activity. Palpitation is a most troublesome feature. The least exertion accentuates it and brings on a feeling of breathlessness. Even when the patient is resting quietly, a certain amount of precordial distress makes him constantly aware of the annoying palpitation. This frequently induces a feeling of apprehension that adds to the discomfort. Insomnia too frequently prolongs the convalescence. Nothing but an inability to fall asleep is apparent. If, during the course of the influenza, gastro-intestinal symptoms have been marked, a profound loss of weight that is with difficulty regained, marks the convalescence.

Complications.—The complications of influenza are far more important than the disease itself. This is true from the standpoint of the resulting mortality and also in regard to the sequelæ. Of these the pulmonary complications take first rank. Bronchitis, bronchopneumonia and lobar pneumonia are most frequently seen. Rarely does the oropharyngeal infection extend beyond the trachea without producing a bronchiolitis or capillary bronchitis. When physical signs suggest these findings, then areas of bronchopneumonia have already developed. Occasionally a severe tracheobronchitis with cough, mucopurulent expectoration, soreness of the chest, fever and protracted weakness mark the extent of the process.

BRONCHOPNEUMONIA.—The onset of this grave complication may be insidious during the course of the influenza; it may be ushered in suddenly after the acute influenzal features have subsided, or it may begin simultaneously with the influenzal invasion. The clinical features of this condition are so characteristic, yet so different from lobar pneumonia, that they are best considered under the caption of influenzal bronchopneumonia.

When the onset is gradual the patient instead of showing signs of abatement of the influenza gradually begins to cough, becomes more apathetic, dyspnea develops, the pulse stays rapid, suffusion changes to cyanosis and chest pains of lancinating type become pronounced. The cough is of a harsh explosive character. As the disease progresses, the paroxysms are often quite prolonged and exhausting. The patient is continually disturbed and soon suffers from the exhaustion produced by it. The sputum, which in the beginning is thick and mucopurulent, soon becomes blood-streaked. Unlike the "rusty" or "prune-juice" sputum of croupous pneumonia, it is distinctly blood-tinged or bloody throughout the whole course of the disease. At times bronchorrhea is so intense as to keep the patient coughing and expectorating almost incessantly. The sputum as the bronchopneumonia progresses becomes thinner and usually contains a mixture of old and fresh blood with mucus, fibrin and often pus.

The early prostration of influenza is accentuated as the bronchopneumonia advances. The weakness is profound, patients oftentimes succumbing to the asthenia resulting from the intense toxemia. Mild delirium may develop, though active or maniacal periods are frequently seen. The dyspnea steadily increases. The respiration varies between 28 and 40 per minute. In severe and fatal cases it may go to 60 and over. The hyperpnea may be maintained for a week or more. As convalesence approaches, the rate slowly and gradually subsides. One rarely sees the sudden fall in rate of breathing that is seen with crisis in severe croupous pneumonia.

The heart rate gradually accelerates. It maintains its rapid rate between 110 and 130 in severe cases for several weeks, in fact, until convalescence is assured. Occasionally a rate of 140 develops, yet the patient may eventually overcome the infection and survive. Most cases that have a favorable outcome begin to show a decline in rate at the end of the first week. Though the temperature be irregular, the pulse in some cases has a tendency to fall to between 85 and 100, which rate it will maintain till complete convalescence sets in. Bradycardia occurs only after complete defervescence has taken place.

The color of the patient so characteristic of influenza in its early stage gradually deepens. Redness and suffusion change to cyanosis and pallor. The blueness in some instances is most intense. This is not due to any change in the oxygen containing power of the red corpuscles. It is due either to the large amount of lung surface involved, lessening thereby the area for exchange of gases, or to the capillary thrombosis in the lung which prevents the blood from obtaining ready access to alveolar spaces. This striking cyanosis may be maintained for many days. It exists frequently in patients with clear sensorium, moderate temperature and good full pulse of moderate rate. It should be regarded, however, with grave suspicion. Though relieved by medical procedures it quickly returns and persists until death occurs. As the infection invades the capillary bronchioles of the lung and lobular involvement occurs, the patient complains of pains in the chest. These are sharp and darting in character, intensified by the breathing. A sense of constriction accompanies the cough. General soreness throughout the chest follows. This is aggravated by the cough. Secondary pleurisy adds to the pain.

When bronchopneumonia sets in suddenly after the acute features of the influenza have subsided, a chill usually marks its onset. The patient becomes suddenly very ill, and the prostration, which marked the onset, returns; vomiting with abdominal distention and distress may take place; hemorrhages are frequent; the temperature rises abruptly and is accompanied by a rapid pulse and increased respiration. All the features of the complicating bronchopneumonia then develop rapidly. In a certain number of cases (the statistics vary so widely as to make them quite unreliable) the beginning of the influenza and of the bronchopneumonia is apparently simultaneous. Coincident with the symptoms of the former signs of the latter are demonstrable in the chest. In this group belong the fulminating cases. These are characterized by suddenness of onset and the overwhelming nature of the toxemia. Death within twenty-four hours may take place. During an epidemic such patients may walk into a physician's office complaining of severe headache or chilliness or profound weakness; or they may be picked up from the street where they have suddenly collapsed, or they may suddenly fall out of the ranks on the line of march. They present the picture of overwhelming exhaustion with deep cyanosis they cough violently and continuously; they expectorate large amounts of frothy, bloody sputum from the intense bronchorrhea, and quickly succumb to the suffocative catarrhal exudation, the edema of the lungs and the toxemia. Such sudden attacks are not seen necessarily among the aged, the weak or the debilitated. Individuals in the fullest health may be stricken without previous warning of the impending disease that overwhelms them.

The earliest physical signs of a bronchopneumonia are fine crepitant and subcrepitant râles, audible at either base or in the interscapular spaces. The breath sounds are weak and distant. There is no change demonstrable in the percussion note. Whispered and spoken bronchophony remains unaltered. With twenty-four hours after the first appearance of the râles, small areas of bronchopneumonia are definable. Relative dulness can be elicited in the affected area. Breathing assumes a distant bronchial character. The whispered and spoken voice are increased. These areas, when first detected are from 1 to 2 inches in diameter. They are most frequently in the right base near the angle of the scapula. They quickly increase in size both by extension and by the coalescence of the smaller areas. In a few days in a typical case, the process has pretty well extended into the middle lobe on the right, or if the left or both sides are involved, it has spread up the posterior aspect of the thorax as far as the spine of the scapulæ. The apices of the lung are spared in the early stages of the process. In a well-developed case when the disease has reached the periphery of the lung, absolute flatness exists. The breath sounds are tubular; marked increase of transmission of spoken and whispered voice are heard. Crepitant and subcrepitant râles do not disappear. On the contrary they are heard in veritable showers over the affected area and extend well into the adjacent unsolidified lung tissues.

The process gradually extends. Sooner or later the physical signs are heard anteriorly at the lower part of the thorax. When both right and left lungs are affected, only the apices have air-containing tissue left. It is remarkable how small an amount of lung is necessary to maintain the respiratory function. In fatal cases of this type, the disease finally invades nearly all of the alveolar tissue. In favorable cases this process may last from one to even four weeks. Resolution may begin at almost any time. This is marked by increase in the number and character of the râles in the area first affected. They become coarser and more bubbling. The flatness gives way to a diminished resonance; the breath sounds grow more distant, whereas the bronchophony loses its intensity. This process is gradual, slower than in acute lobar pneumonia, the râles often persisting for some period of time. In delayed resolution the usual features of weak bronchial breathing with moist râles are demonstrable for a variable length of time depending upon the rapidity of the changes in the lung.

As previously stated all degrees of the process are found from a small patch with only fine râles in one base which lasts but a day or two, to a widespread lobular consolidation with coalescence, that takes weeks for the disease to run its course. In protracted cases areas of liquefaction necrosis occasionally occur giving rise to solitary or to multiple pulmonary abscesses. The presence of the solitary abscess when of sufficient size is determinable by the usual physical signs of this condition. The rupture of such an area into a bronchus gives rise to the expectoration of thick, yellow, foul-smelling sputum, with amelioration of symptoms. Such abscesses when thick-walled and close to the hilus sometimes fail to collapse, eventually forming the basis for secondary osteoarthritic changes. Multiple abscesses may range from miliary abscesses scattered like tubercles throughout the lung, to a smaller number the size of hazelnuts. Such findings were not infrequent on the postmortem table during the recent epidemics. The physical signs of the multiple small abscesses are quite indefinite. The persistence of physical signs of a resolving bronchopneumonia with the septic temperature, elevated pulse rate, profuse sweating and purulent expectoration generally suggest the condition. The x-ray sometimes may be necessary to disclose them. The course that the bronchopneumonia takes depends first of all, as already indicated, upon its duration. This is so variable that nothing typical of the condition really exists. A few features however are quite constant and deserve mention.

The course of the temperature while quite irregular is nevertheless frequently marked by a pseudocrisis. This is seen whether the final termination is by lysis or crisis. In a series of 160 consecutive cases of bronchopneumonia in civilian practice, 119 or 74.3 per cent. fell by lysis and the remainder by crisis. Reports from military camps show the proportion that fall by crisis to be slightly higher. The pulse rate falls gradually with the temperature. A rapid rate may be maintained for a considerable period of time. Rates from 120 to 130 persisting for several weeks have been observed. A bradycardia as low as 40 may occur; however, more commonly a tachycardia persists following the severe protracted cases. The interesting leukopenia that usually accompanies the influenza may persist when the bronchopneumonia sets in. Such cases usually do badly. In most instances a leukocytosis develops, counts running between 12,000 and 30,000. The average is about 15,000. The increase is doubltess due to the secondary invasion of pneumococci or streptococci.

Other Complications.—Croupous pneumonia is a very uncommon complication of influenza, though it is occasionally seen. Its symptoms and physical signs correspond to those described in the chapter under Lobar Pneumonia. It might be said that the onset of these cases closely resembles that of the bronchopneumonia except that an insidious onset is rarely seen. In these cases an apical localization is frequently encountered. A leukocytosis is uniformly present. The pulse rate except in cases terminating fatally does not become as rapid. Crisis is the common form of favorable termination yet a larger number fall by lysis than in uncomplicated croupous pneumonia. The infecting organism in these cases is the same as occur symbiotically in all the influenzal pulmonary complications.

Larnygitis deserves mention as the most frequent individual complication. Hoarseness, from a mild degree to complete aphonia with obstruction, occurs in a large proportion of all cases. It is perhaps the most frequent cause of early cough. Together with the pharyngitis and tracheitis it produces the irritation that gives rise to the harsh, rasping cough common in influenza. So severe may the condition become as to arouse the suspicion of the possibility of a diptheritic infection. Stridor, tugging respiration, retracted episternal notch and air hunger may suggest the need of intubation or tracheotomy. The appearance of the larynx varies. In most cases there is a swelling of the mucous membranes of the posterior wall, with hyperemia of the false vocal cords. Frequently the true cords are injected and show marked subglottic swelling. Generalized redness and vascular injection of the mucous membranes with edema are observed in the severe cases. Laryngitis may be protracted, persisting long after the temperature and pulse have reached normal, and general symptoms have subsided. The mild cases subside in twenty-four hours.

Coryza, though frequently spoken of as a symptom, should be classed as a complication of influenza. Redness and dryness of the mucosa of the nasopharynx are the rule. Excessive secretion is uncommon. In reviewing a series of 180 consecutive cases gathered from all sources, only 22 had a coryza. Levin, reporting the frequency of coryza in children in whom it would be expected to be common, found 13.8 per cent. in 1918 and 24.2 per cent. in 1920 suffering from profuse nasal secretions. Many observers hold a contrary view to this, some going so far as to consider a rhinitis one of the usual features of the onset. It is a fact, that in individuals who have previously suffered from a coryza with serous secretion, influenza sets in abruptly; however during the past epidemics the redness of the conjunctiva, nares and pharynx was most generally associated with dryness and glistening appearance that differs markedly from mucous membranes bathed with secretions. The intense frontal headaches have been ascribed to the rhinitis. This is not usually true in view of the fact that the pains at onset are just as severe in the absence of catarrhal symptoms. Certain cases of severe and persistent headaches occur when infection from the nares extends into the accessory sinuses. The antrum, the frontal and ethmoid, are most frequently involved.

Sinusitis generally occurs when the acute influenzal symptoms are subsiding. The inflammation is quite active, giving rise to intense recurring paroxysms of pain. Rarely a pansinusitis is seen. Chronic discharging sinuses are troublesome conditions enduring sometimes for years after the acute features of the disease have disappeared. These foci may harbor the organism of the original infection for an indefinite period of time.

Otitis media occurs following inflammation of the eustachian tube. The onset is quite acute with pain, sudden elevation of temperature and impairment of hearing. The tympanum is hyperemic. Hemorrhagic blebs and even bleeding may take place. Immediate paracentesis gives relief. A serohemorrhagic discharge usually follows and remains persistent as a rule for some time. Later it becomes purulent. When the inflammation has extended into the mastoid cells a serious complication must be dealt with. Otologists have pointed out during the recent epidemics that the features of acute mastoiditis due to influenza present a picture quite different from the usual signs of mastoid disease caused by the pneumococcus, streptococcus and staphylococcus. These organisms sooner or later, however, predominate.

Eye complications outside of the conjunctivitis are exceedingly rare. A few cases of corneal hemorrhages have been reported by ophthalmologists. Dacryocystitis is occasionally seen. The optic nerve may be involved in a retrobulbar neuritis.

Pleuritis apart from that occuring along with the pneumonia is commonly encountered. It is characterized by the usual symptoms of pain on respiration, elevated temperature, great restlessness, sharp, hacking cough and dyspnea. Effusion and empyema may follow. The acute pleurisy may develop at the outstart of the influenza, during the course of the disease or after convalescence has set in. As a rule it is most violent when it occurs at the outstart of influenza. It sets in abruptly with great pain and prostration. Friction rubs may be heard over the affected side. They are frequently widespread. In this type sudden rapid effusions take place. The exudate is thin and yellowish and exerts great pressure on the lung. As soon as it is withdrawn by paracentesis it has a tendency to form again. Inasmuch as little or no fibrinoplastic exudate forms, the tendency to adhesions is slight. Even rib resection is of little avail in the early stage. The rapid refilling of a pleural space causes great pressure to be exerted on the mediastinal tissues. Under such conditions "ramrodding" over the heart, great vessels, bronchi and other tissues may give great distress with symptoms of collapse and death. If no effusion occurs, the acute pleuritic symptoms may last from a few days to several weeks, even, beyond the time of general convalescence. Pleurisy developing during the febrile stage after influenza is fully established, is with few exceptions of less severe type. Though the pain may be as intense, there is less collapse. Serous and at times serohemorrhagic exudates occur. These effusions are seldom extensive in character. Fluid withdrawn is rich in leukocytes and large mononuclear cells, contains some fibrin and occasionally red cells. Phagocystosis is observed at times. If secondary infection intervenes, an empyema forms with the usual physical signs of that condition. During convalescence after the febrile period is well past, acute pleurisy may develop. Slight elevation of temperature occurs, with cough, some dyspnea and pain.

Much difference of opinion exists in regard to the likelihood of acute pleural involvement without pneumonia or at least a bronchiolitis. On physical examination friction rubs are often detected without the discoverable presence of lung involvement. Even effusions from serous to purulent are demonstrable in the absence of physical signs of lung involvement. On the autopsy table these clinical observations are not entirely verified. A more or less extensive pneumonia process is present wherever a pleuritis is found, whether it be but a small area of fibrinoplastic exudate or an extensive purulent effusion.

The circulatory system is not a frequent seat of complications in influenza. The heart resists the toxins of the disease remarkably well. Acute endocarditis is very rare. Myocardial changes though seen postmortem are rarely discovered during the course of the disease. Pericarditis frequently occurs as a part of the complicating pleurisy but is rarely observed independently. Arterial changes that have been reported are probably due to an exacerbation of a previously existing endarteritis, produced by the complicating organisms or their toxins. Venous thromboses may occur in any part of the body. They are most common in the femoral vessels or one of its branches. Mesenteric and pulmonic thromboses are less frequent. They are always of grave significance. In the abdomen intense pain with meteorism and gastro-intestinal disturbances are disturbing factors. In the lung signs of pulmonary infarction with the customary physical signs give a serious aspect to the disease.

Though neuritis occurring both during and after an influenzal attack is probably one of the conditions most frequently met with, it should not properly be classed as a complication but rather as a symptom of the disease. It is referred to elsewhere. Psychoses usually resembling the manic-depressive type are not infrequent, particularly where a congenital predisposition thereto exists. These mental states usually appear in the latter part of the attack or immediately following it. The prognosis is generally favorable.

Influenzal meningitis is a rarity. The author has not seen a single instance in the epidemics of the past few years. Such cases are evidently more frequently reported among children. Pure cultures of the influenza bacillus are recovered in spinal puncture.

As in the pandemic of thirty years ago, so too in the one just past, lethargic encephalitis has occurred in epidemic form. The author has seen in the last two years over 160 cases of the disease. It should not be classed as a complication, for it is not infrequently seen in patients who have not suffered from influenza. It has none of the characteristics of influenza, unless the mild sore throat and the head pains that are present so often at the onset may be considered as such.

Of the urinary complications the usual scanty urine, slight amount of albumin, and few casts that occur in acute febrile states are found. Severe nephritis is rare. Hematuria is occasionally observed. Several cases were observed in individuals with previous histories of renal calculi.

In the reproductive system the complications are of a serious character only in the female. Here menorrhagia is common and produces an anemia that in a few instances has required transfusion. The pregnant uterus is a grave condition. If the patient is under three months pregnant early abortion is a fortuitous circumstance. As a rule most women who have been pregnant for a longer time miscarry during the course of the illness. Even then the condition is a serious one. If the child is of a viable age and is born during the illness it rarely lives. Unless the influenzal attack is a very mild one, the prognosis is always doubtful for the survival of both mother and fetus.

It has been generally supposed that tuberculosis commonly follows an attack of influenza. It is doubtful whether the incidence of tuberculosis has increased because of the last pandemic. Undoubtedly influenza may aggravate a tuberculous condition, or it may activate a fairly quiet tuberculous process. Yet a great many cases of tuberculosis which are supposed to have resulted from an attack of influenza are in reality the unresolved signs of an influenzal condition. In a suspicious case careful temperature observation, sputum examinations and fluoroscopy should determine the facts.

Treatment.—The treatment of influenza may be considered under three headings: (1) Preventive; (2) symptomatic; (3) serum and vaccine. The management of the various complications, with the exception of certain phases of bronchopneumonia will be found in the sections of TICE given over to these specific conditions.

In spite of the fact that much has already been attempted in the matter of preventing an attack of influenza in the individual, nothing tangible exists at the present time. Under prophylaxis the question of preventing the spread of the disease in epidemics was discussed. Even when an epidemic threatens a locality such measures seem unavailing. In a general way, when the disease once flourishes, the methods generally employed to check its wide diffusion have a relative value. However, so far as the individual is concerned, the physician is at once at a loss to know what he may recommend. **General hygienic measures** such as sufficient rest, cleanliness of hands, mouth and teeth, fresh air while at work and during sleep, regulation of meals and bodily functions, wholesome food, freedom from anxiety, all these and many other ordinary regulations are essential in establishing resistence to influenza.

Quinin, the **salicylates** and **alcohol** are chief among the medicinal measures that have been used to prevent influenza. To these may be added the innumerable worthless proprietary remedies. With the danger that always exists of generalizing from some particular experience, undue credit has been accorded various remedial agents. Reliable statistics and unbiased experience tend to show that all are of equal merit. As often as they tend to assuage fear of the disease in an apprehensive neurotic, just as likely are they to give a false and dangerous sense of security in another. And let it be said here: It is a question whether or not the free use of such drugs may not reduce the normal metabolism of the individual and make him more susceptible to a prevalent disease.

The properly made and carefully adjusted **gauze mask** has perhaps relative preventative value. It is **not a safeguard.** Its universal use is to be deprecated.

During the epidemic just past ample opportunity was afforded to test the preventive value of **vaccines.** This has already been spoken of in an earlier paragraph. In the present state of our knowledge, their use **cannot be recommended** on any sound basis. However should the cause of influenza be definitely determined, the rational procedure for prevention may be found in preventive inoculations either of vaccine or antitoxic serum.

TREATMENT OF SYMPTOMS.—*General Methods.*—The management of the individual case depends largely upon the condition of the patient when first seen, and also on the point of view and previous experience of the practitioner. Where no specific remedy exists, no hard and fast rules can be formulated for universal adoption. Therapeutic indications should be sanely met and indiscriminate and overmuch medication avoided.

The patient should be **put to bed** at once and kept warm. **External dry heat** in the form of water bottles and heating pads should be applied. Warm bed clothes are essential. The exposure of the patient to cold distinctly increases the dangers of complications. The room should be kept reasonably warm, about 65° F. (18.3° C.). **Fresh air** should be plentifully supplied. However, excessive exposure to cold air, variations of temperature in the sick room and the unheated room are to be avoided. Cold, dampness and stuffy quarters predispose to complications in the respiratory tract.

At the outstart a **purge** is advisable. Though **calomel**, either 2 grains (.13 gram) in divided doses or a single dose of 5 grains (.324 gram) has been extolled for centuries as the desirable method of producing prompt catharsis, it possesses no particular advantage over the early administration of an ounce (31.10 grams) of **oleum ricini**, an ounce of **magnesium sulphate** or of an equivalent saline. Afterwards the bowels should move daily with the aid of a **mild laxative** or a **small tap-water enema.**

Drugs.—The **salicylates** offer one of the most useful means of combating the early symptoms of influenza. **Sodium salicylates, acetylsalicylic acid** or **salol** in 10-grain (.65 gram) doses with an equal amount of **sodium bicarbonate** given every two to three hours for four doses, will usually alleviate the headache, lumbar and generalized pains. Sometimes the addition of from 2 to 5 grains (.13 to .324 gram) of **phenacetin,** or of one of the numerous **coal tar derivatives** may be necessary. If the prostration is marked, this should not be done except with great caution. It is far preferable in some instances to give small doses of **codein sulpate,** ⅛ to ½ grain (.0081 to .0324 gram), or **Dover's powder,** 1 to 5 grains (.065 to .324 gram), and to repeat as often as needed **until the** more intense pain subsides.

Quinin is largely employed. It is given in rather large doses, 5 to 15 grains (.324 to .972 gram), every three hours. Some believe in its specificity, especially in preventing grave pulmonary complications. As high as 30 grains (1.95 grams) are given in one dose for abortive effects. It may be said that quinin rarely gives much relief from the pains. Its use should be closely watched, as it frequently produces gastric irritation and also has a tendency to aggravate auditory complications. After the acute symptoms have subsided no medication is necessary. Only the complications as they arise require attention. Treatment of them will be found under their special chapters.

Hydrotherapy.—The patient should receive a **daily tepid sponge bath.** If the head pains are excruciating, as is so often the case, **hot stupes to the forehead** may be tried. These are usually more grateful than cold water or the ice-bag. A **mustard foot bath** may be given, especially when the patient is chilly. Frequent bathing for high temperature is unavailable. The baths, however, have a decidedly stimulating effect upon the sensorium and the depressed vasomotors, and for this purpose may be employed as often as every four hours. The temperature should be between 90° and 95° F. (32.2° and 35° C.).

For the stuffy sensation and difficulty that the patient experiences with breathing, a few drops of **adrenalin solution** dropped into each nostril at intervals gives relief. **Hot fomentations**, especially if sinus involvement occurs, are a valuable adjunct.

Mouth washes, throat irrigations and **gargles** should be regularly employed. Normal saline solution or mild alkaline antiseptic solutions are preferable for cleansing and bathing the inflamed mucous membranes.

COUGH.—In many instances a cough mixture is indicated, especially when bronchitis, tracheitis or laryngitis produce much irritation. **Ammonium chlorid, terpene hydrate** or **guaiacol carbonate in syrup of tolu** is usually sufficient. When the cough is distressing, **syrup of codein,** or **syrup of Dover's powder** may be added for their sedative effect.

COLLAPSE.—When signs of collapse threaten, stimulants should be employed in full measure, chief of which are **camphor in oil, caffein sodium benzoate** and **strychnin by hypodermic.** The value of the latter is somewhat doubtful. Its only indication lies in its possible action in increasing the secretory activity of the suprarenal glands. The cautious use of adrenalin by hypodermic should always be considered; 5 to 15 minims (.3 to .92 c.c.) of the 1 to 1000 solution further diluted may be given subcutaneously every two to three hours when signs of profound prostration threaten.

The use of **saline hypodermatoclysis** or of **transfusion** is indicated at times. If the danger of imposing greater strain on the circulation can be disregarded, then the administration of 500 c.c. every four to six hours in cases presenting the features of a "toxemic shock" is useful. In the less prostrated case where high temperature, dehydration and intense intoxication have combined to make for an intense exhaustion, the Murphy drip method of administering the saline solution is to be employed.

PAIN.—The measures already described will in the large majority of cases alleviate pain. In the occasional case, suffering becomes so unbearable that **morphin** must be used. This is always best combined with a small dose of **atropin.** Pain due to pleurisy often requires such measures. First, however, counterirritation with mustard plasters, icebags and strapping with adhesive tape should be given a fair opportunity to afford relief. Joint pains are so rarely due to arthritis that local measures of fixation and heat do not give the relief that **analgesics** administered orally do. The pain due to neuritis, especially the postinfluenzal type, is most difficult to treat. Opiates in all forms should be avoided. Their use may readily lead to drug addiction. **Blisters** along the course of the nerve, **liquor potassii arsenitis, sodium cacodylate, iron arsenite,** the **iodids,** and the **nitrites** should first be tried. The specific value of any treatment may be judged by the array of medication recommended. If these do not suffice, then **nerve stretching** or **nerve injection** may be attempted. One fact, however, should never be lost sight of: A careful search should repeatedly be made for some other source of the neuritis. The patient's lowered resistance following influenza only too frequently permits an inactive focus to spring up or revive and initiate the symptoms of the neuritis.

Diet.—**Fluids** should be plentifully given during the course of the disease. Fruit juices, albumen water, milk, barley water, and clear broths are well borne. In mild cases eggnogs, oatmeal gruel, gelatin and custards may be added. A daily use of from 1,500 to 2,000 calories is ample. This diet should not be increased materially until at least twenty-four hours after all acute symptoms have subsided. Then a soft diet may be substituted and the caloric intake augmented. **Water** may be freely given at all times, and the patient should be encouraged to drink plentifully. **Alcohol has no especial value** and its use is not to be encouraged. Champagne is frequently recommended when anorexia and nausea occur. Charged waters are equally as efficacious.

When gastric symptoms become troublesome, all nourishment should be stopped. Small quantities of fluids—not more than one ounce every hour or two—may be given. Chipped ice will allay the thirst. Medicinal treatment in gastric complications is of little or no avail. A great number of preparations have been used with success by their numerous sponsors, all of which make their specific value the more doubtful.

Vaccine Therapy.—During the past epidemics vaccines of every sort and description were used. In a few the influenza bacillus alone was given. In most instances a mixed stock vaccine composed of influenza bacilli, pneumococci, streptococci and staphylococci were employed. Without more definite data as to the causative organism nothing can be expected from the use of the vaccine. Though startling results have been reported in some instances, just as remarkable recoveries occur without their use and even without medication of any kind. Statistical evidence on the subject is not trustworthy. Therefore, the use of vaccines at the present writing is **not to be recommended.**

Serum Therapy.—McGuire and Redden's procedure has been accepted with great enthusiasm in some quarters. The injection of pooled convalescent sera has certainly some theoretic value to recommend its further use. Recovery from the disease under different conditions and with variety of forms of treatment has been so frequently observed that the author is inclined to the impression that thus far "**experience is fallacious and judgment difficult.**"

Venesection—Though the history of disease abounds with instances of the futility of blood-letting, it still seems to enjoy favor in many quarters. The temptation to bleed the ashen gray and cyanotic influenza patient whose pulse is full and not much accelerated, who shows no signs of cardiac failure, who is not dyspneic yet in whom signs of anoxemia portend a probable dissolution, has not waned in recent epidemics. Frankly the author **has never seen good come of venesection.** When it is followed by transfusion of blood some temporary improvement is often seen. In fact the author might be persuaded to say that he has observed it tide a few over a critical period. Yet who can say that they would not have survived without this procedure? The intravenous use of 10 per cent. glucose solution, 100 to 200 c.c. given every four to six hours after the withdrawal of an equal amount of blood, is worthy of trial. Whether or not pulmonary edema has developed and even with the advent of deep cyanosis, this method has many enthusiastic advocates. Temporary improvement also occurs with this procedure. Yet its ultimate value seems to be quite doubtful to the author.

The treatment of the psychoses, complications of the pleura, genitourinary tract and special sense organs is left to the chapters in TICE dealing with those conditions.

The asthenia that occurs during the course of the disease and also when convalescence has set in is difficult to cope with. When the influenza is at its height, the administration of **camphor, aromatic spirits of ammonia, caffein** and **adrenalin** may be tried. In the stage of convalescence the hypodermic use of **iron, nux vomica, arsenic** and the **hypophosphites** usually increases the patient's strength.

Pathology.—A description of the pathology of influenza must necessarily include a consideration of the attendant bronchopneumonia that is the cause of death in the vast majority of cases. Death rarely, if ever, has been known to result from the influenza, so that the pathologic picture of the early stages is seen during an epidemic only when death has occurred from another cause. The author has seen 2 such cases, one during each recent epidemic. In one instance, death occurred in a young woman as the result of an automobile accident. This individual had complained of symptoms in the morning while at college. Twelve hours after she had been told that she had influenza, and while returning to her home some thirty miles away, she met with a fatal accident. The other case occurred during the last epidemic in a man of forty-six who, following an altercation, was shot through the head and died instantly. The patient had been ill, as the records show, with moderately severe symptoms of influenza for about thirty-six hours. In each of these instances the outstanding feature, at rather incomplete autopsies, was an intense inflammatory reaction of the respiratory tract. The mucous membrane, the nares, pharynx, larynx, trachea and bronchi of large dimensions were red and swollen and covered in patches with mucus. There was injection of the conjunctivæ and all the membranes had the appearance characteristic of marked swelling and congestion. In both instances small punctate hemorrhages could be seen here and there beneath the tense mucous membrane ready to burst through the mucosa. No free blood was visible, though bleeding might readily have occurred. The mucus was mostly clear, though in the nares it was beginning to show a slight opalescence and yellowish tinge. In the bronchi of finer caliber less redness was visible, though in areas begining swelling of the mucous membrane was seen. There were no visible hemorrhages or signs of capillary congestion. The alveoli were normal. Throughout the remainder of the bodies no abnormal findings were disclosed, with the exception that in the young woman who died within two hours following the automobile accident and whose temperature three hours previously had been 104° F. (43.3° C.), definite swelling of the adrenals was observed with a few hemorrhages, pin-head in size, scattered throughout the cortex of each gland.

The histological picture in these 2 cases resembles closely, though to a less degree, the findings in the upper respiratory tract of those who died from the complicating bronchopneumonia. This will be described more in detail later. One feature is worthy of note, namely, that in these instances of early invasion, small, round cell infiltration was rarely to be observed beneath the mucous membrane. This is in contradistinction to what is seen in the fulminating cases, where a necrotizing process may be observed rather early. Exfoliation of the mucosa was also not observed.

This picture of early invasion is probably dependent upon a single etiologic organism, the nature of which has not been definitely determined. The acute inflammatory invasion is similar in the upper respiratory tract in all cases that have came to autopsy. The degree of the tracheobronchitis would vary with the age of the lesion. Changes in mucous membrane, ulcerations, areas of hyalinization are all dependent upon the extent and duration of the process. In fact, it is remarkable how long the picture of an early tracheobronchitis may persist. However, another factor invariably alters to some extent the picture of the earliest process. This factor is the type of the secondary bacterial invaders, which, depending upon the organisms that preponderates, undoubtedly affects the gross as well as the microscopic picture.

From the foregoing, it would seem that the pathways of invasion in influenza and influenzal bronchopneumonia are probably by the way of the upper respiratory tract, through the bronchi and into the finer pulmonary capillaries and alveoli. This corresponds with the general observations of those who have attempted to reproduce the disease in volunteer subjects and in lower animals.

In previously healthy individuals coming to autopsy, the surface of the body especially in the dependent portions presents a purplish appearance that is frequently tinged with a slight waxy, yellowish color. This is not to be confused with those that have had an icterus complicating the bronchopneumonia prior to death. When the body lies in the dorsal position, the postmortem hypostasis of the skin is an outstanding external feature. The lips and nostrils are frequently covered with herpes or with dried bloody exudate and frothy mucous often pours forth for some time after death. The blood-vessels frequently stand out prominently. In rare instances diffuse emphysema of the skin is observed. This may be so intense as to distend the loose tissue about the face, neck, axilla and genitals, giving the patient an appearance not unlike that of a drowned person. The air in the skin crackles under the examining finger. The chest is usually full and distended as is also the abdomen, especially if meteorism has been marked prior to death. Rigor mortis sets in early, and is so intense at times as to be one of the striking postmortem features of the disease.

On section the blood has a deep purplish-red appearance. The congestion of all the vessels is further demonstrated by the freedom with which the cut surface bleeds. There is nothing characteristic about the fat or subcutaneous tissue. On opening the abdominal cavity, the intestines are usually distended, and their blood-vessels are engorged. Capillary hemorrhages are frequently seen. Sometimes a small amount of serosanguineous fluid is found in the abdominal cavity. The liver and spleen are both frequently enlarged and extend as a rule somewhat below their usual position in the abdomen. This is in part due to the lowering of the diaphragm as a result of the distention of the lungs, or of fluid in the pleural cavities.

The abdominal muscles as a rule show very little change. Occasionally an acute myositis is met with. In protracted cases areas of Zenker's necrosis are found, especially in the abdominal muscles. Areas of small round cell inflammation frequently occur. Abscess formation is rare. The commonest change on gross examination is a pale brownish red muscle that microscopically reveals the fibers to be swollen, their striations scarcely visible and showing here and there areas of regeneration.

The spleen is slightly enlarged, weighing on an average about 300 grams (.66 lb.). Marked increase in size may be seen. The spleen is soft, sometimes mushy in consistency. The external color is darker than usual with more of a purplish cast. On section it is friable and bloody. The trabeculæ are somewhat effaced, due in part to the swollen and bloody condition of the pulp and in part to a toxic necrosis of the reticulum, with its areas of hyalin degeneration and masses of disintegrating cells.

The liver is generally increased in size. The color is practically normal. The capsule is not thickened. The cut surface in the enlarged organ is bloody though the liver lobules are paler than normal. Microscopically there is cloudy swelling. Frequently various stages of liver cell necrosis are met with, the conspicuous changes appearing in the center of the lobule. The bile canaliculi are often quite prominent, showing here and there areas of necrosis. This may account for the complication of jaundice observed clinically in certain instances.

The stomach and intestines present no characteristie changes. Petechiæ and suggillations among the engorged vessels are met with.

The kidneys as a rule are slightly enlarged. There is nothing unusual about the findings either in the gross or in section. Cloudy swelling is present as a rule, the vessels are congested and in rare instances petechiæ are seen, especially about the pelvis. Nephritis is demonstrable in a variable number of cases. This is probably due to the secondary invading organism.

The suprarenals usually appear normal. Congestion occasionally is seen in the freshly sectioned gland. In a few instances petechial hemorrhages are seen in the medulla. This was observed once in a case in which death resulted without pulmonary complications. The remainder of the abdominal organs and tissues present signs of toxic degeneration to varying degree. Hence there is nothing noteworthy in them with the possible exception of the uterus.

In pregnancy influenza is a most dangerous complication, often resulting in early death. The uterus and placenta are usually involved. Grossly the two striking features are the tremendous congestion of these organs and the areas of hemorrhage. Microscopically no changes are seen in the placenta except, perhaps, early hyalin changes and some areas of thrombosis in the vessels. In the uterine muscle fibers marked edema with disappearance of the muscle striæ and pyknosis of nuclei appears. In one case areas of coagulation necrosis were observed.

Section of the thorax gives a picture somewhat suggestive of what is revealed upon opening the abdomen. The dark fluid blood pours from the distended vessels in great amount. The lungs are voluminous and on removal of the sternum protrude into the space, often obliterating the pericardial area. The variegated color that the lungs present through the translucent pleura are most striking. All shades are seen from that of the normal lung tissue to the deep bluish red and brown zones that protrude above the surface and give the lung an irregular shape. Added to this are numerous smaller areas where petechiæ and suggillations have mottled the lung surface. These changes are most marked in the lower portions, the upper anterior parts being the last to be affected. The pleura may be dry or there may be varying grades of exudates present, serous to seropurulent on the one hand, serofibrinous to hemorrhagic on the other. Large amounts are rarely encountered. Pleural adhesions and empyemata occur chiefly in long-standing and protracted cases. Subpleural hemorrhages are always in evidence.

The pericardium is generally smooth and may contain a slight amount of straw-colored to blood-stained fluid. Here, too, petechiæ may be seen. The heart distends the sac, the right ventricle being almost always dilated and filled with "agonal blood," while the left too is distended but to a lesser degree. The endocardium is generally smooth, an active endocarditis being of rare occurrence. Punctate subendocardial hemorrhages are very common and are found in all the walls even extending among the papillary muscles. As the lungs are removed the glands at the root of the lungs appear enlarged and congested. They are quite soft and on cut section fluid escapes freely from them.

Sometimes hemorrhagic areas are seen as in other tissues. Histologically the lymph spaces contain erythrocytes, mononuclear cells, some fibrin, and bacteria, and when the disease is associated with a polymorphonuclear reaction, large numbers of polymorphonuclear cells. Active phagocytosis may be seen in all the sinuses. The blood-vessels are packed with cells. Here and there thrombosis may be seen.

The trachea and large bronchi are always injected and edematous. On section the mucous membrane is bathed with a frothy serosanguineous fluid. The mucosa is the site of a catarrhal process into which numerous hemorrhages have taken place. In areas exfoliation occurs leaving bleeding, denuded surfaces. There may furthermore be seen areas where an intense necrotizing process has left deep ulcerations in the wall. These are usually small, though extensive areas are sometimes found.

When the lung is removed it is firm, dense and voluminous. It has a tendency to retain its form, though not to the extent of a completely hepatized organ. It cuts easily, the surface bulging out in the affected areas and the uninvolved portions collapsing. This gives an irregular appearance to the cut surface. A serosanguineous fluid at once flows freely from every portion of the cut lung, mixed here and there with frothy mucus that escapes from the cut bronchi. As the fluid is wiped away the dense and darkened areas stand out with great prominence. The surfaces present a great variety of colors. Viewed *in toto* one sees every shade from the deep purplish, brownish hues of the dependent areas at the base to the pale grayish pink of smaller unaffected superficial portions of the anterior parts of the lung. Here and there are interposed dark reddish areas in which extensive hemorrhages have occurred. In a few instances vesiculated elevations are seen where interstitial emphysema has allowed air to accumulate under the pleura. At times small amounts of fibrinous exudate appear on the pleura, though this is an exceptional rather than the conspicuous feature of the gross lung. More frequent are recent subpleural hemorrhages which appear as bright red splotches of varying size and shape at almost any place of the lung. The lobules stand out quite prominently. This is due to the outlines produced by the swollen connective tissue and the engorged blood-vessels. Wherever extensive consolidations exist the dark areas in the cut surface somewhat obscure the outlines of the lobule so that the neighboring hyperemic pulmonary tissue merges gradually with the denser areas. In lungs in which resolution has begun, the coloring is less vivid, the exudate is thicker and less fluid exudes on section. In these cases abscess formation is found. An unusual condition is that described in a few instances where the cut surface of the lung presents a more uniform reddish gray appearance throughout which were scattered great numbers of small pale yellowish areas from pin-head to split-pea size. The surface resembles somewhat the appearance of a lung seen in miliary tuberculosis. These minute masses are miliary abscesses scattered throughout the lung.

In instances where diffuse subcutaneous emphysema existed antemortem, a similar condition is found in areas through one or both lungs. The original lesion is produced by the rupture of one or more distended alveoli, whence the air escapes along the interstices of the lung to the hilum and up into the tissues of the neck. Occasionally in the midst of a dense voluminous lung one finds areas of pulmonary collapse. As a rule these are small, yet atelectasis of an entire lobe has been described.

As might well be predicted in a disease that extends progressively from the larger to the smaller ramifications of the bronchi, the process finally spreads into the alveoli. The small tubules cannot resist the extension of so intense an inflammation; hence the pulmonary parenchyma is quickly involved. Though this fact has not been proven in influenza, it is safe to conclude by analogy to similar pulmonary conditions that the disease is bronchiogenic.

No uniform histologic picture occurs in the lungs in influenzal bronchopneumonia. Descriptions though tallying in general, vary in the detailed reports. The great variety of the secondary invading organisms is probably the chief reason. Furthermore the duration of the primary influenza as well as the severity of the inflammatory pneumonitis determines the ultimate pathologic picture. All observers are agreed that the process is preëminently a lobular pneumonia, though in most respects it is unlike bronchopneumonia, even though it is generally understood to be similar. The paucity of fibrin, the tendency to hemorrhagic exudation, polymorphonuclear and mononuclear infiltration and areas of hyalinization are the most commonly accepted features of the process. On the other hand lung tissue rich in fibrin, cases of pure croupous pneumonia, and diffuse suppurative processes are often encountered.

A subject who has succumbed early in the course of the disease will not present the pathologic picture of the one whose lung is examined three weeks after the onset of the pneumonitis. Between these two extremes the process varies greatly, though early inflammation and a later purulent process may coëxist in the same lung. Unlike other forms of pneumonia stages of hepatization cannot be described. The features of influenzal bronchopneumonia are fundamentally an inflammatory reaction distinct from that seen in any other disease. And this, too, in spite of the fact that the secondary invaders may be the same forms of pneumococci that produce a typical lobar pneumonia.

The alveoli lose their shape, becoming either distended or collapsing altogether. The lining epithelium is lost or added to the detritus that distends its wall. Here is seen serum, blood-cells, rare strands of fibrin and occasional mononuclear leukocytes. The pulmonary arterioles are engorged and stand out prominently in the edematous connective tissue of the lung. In places the alveolar and bronchiolar wall shows areas of necrosis such as appear in the larger bronchi after desquamation of the lining mucosa has taken place. Often the bronchioles are completely destroyed and in their place are seen necrotic tissue serum, cells and organisms. At first mononuclear leukocytes are present. Later, however, especially depending upon the organism, the polymorphonuclear cells predominate and frequently are actively phagocytic. These areas of destruction and exudation give rise to areas of consolidation that have been variously described by many observers. However they may be interpreted, they form the basis for the primary inflammatory process or deposit which is well termed a pneumonitis. In this all subsequent changes occur either in the form of resolution and repair or further suppuration and necrosis.

Historical Summary.—A considerable difference of opinion exists as to the year in which the first epidemic of influenza occurred. August Hirsch in a "Chronological Review of Epidemics of Influenza" places it in the year of 1173. The data from which he draws his conclusions speak of epidemics of severe coughs, "singularly pernicious," that ravaged England, Germany, Italy and France in that year. Of earlier epidemics no reliable information can be found, save those that refer to pestilence that destroyed many people, or diseases that spread with great rapidity over the face of the earth and from which there was great mortality. That such epidemics must have occurred cannot well be doubted. To definitely give credence to the assumptions of historians such as Leupold, Haeser, *et al.*, that these pestilences were true influenza, has no real medical value. However, from a historical standpoint much material for interesting speculation is at hand. Whether or not the Greek army before Troy was stricken with influenza or the report of Diodorus Siculus on the epidemic that "killed off the soldiers murderously" at the siege of Syracuse in 395 B. C. refers to this disease, can remain only an unsolved question for conjecture and discussion. Likewise flimsy evidence may be conjured up from the writings of Hippocrates, Livy, *et al.*, to show that influenza existed in ancient times. Though there appear to have been epidemics of "catarrhal fever" in the seventh, eighth, ninth, and tenth centuries, records at hand afford no certain proof that these were identical with what is regarded as influenza to-day. Plague, cholera, smallpox, "sweating sickness" and many other diseases occurred with pestilential virulence. But the records of all exist chiefly in a description of the enormous mortality that resulted with little or no mention of the symptoms or morbidity that obtained at the time.

That influenza must have existed with variable virulence is evident from later authentic writings. Though most historians speak of the disease as attacking many, but killing the old and decrepit chiefly, it is highly probable that in the great pandemics of early history many of the young and virile were victims of the complications and sequelæ of the disease. In fact our recent experience with influenza compares to and in a measure substantiates this. It reveals how thousands may be stricken and hundreds die "even between sunrise and sundown."

In the year 1323 Hirsch believes the second great epidemic to have occurred. Gluge agrees with him in this and also affirms an epidemic that developed four years later in 1328. The most reliable data in confirmation are the writings of Buoninsegni, who speaks of an *influenza di freddo* (an influence of cold) that spread "from person to person, through cities, into districts and into the interior of the country." In this he refers to an epidemic supposed to have occurred in 1358. Most historians, however, regard the earlier ones of that century more probable than the one to which this passage refers. One is more inclined to regard it as a sporadic outbreak of the disease.

In 1387 indisputable records of influenza are found. It was observed by competent chroniclers in Italy, France and Germany. They all speak of a disease that ravaged these countries. Beginning in Florence, it spread with great rapidity, prostrating nine-tenths of the population. The symptoms were "cold in the head, cough, headache, oppression of the chest, fever and sometimes delirium." Attacks lasted from four to five days. The afflicted were treated with camomile tea, sweating and low diet. Evidently the mortality was not great, for all writers speak of many stricken, yet few succumbing to the disease.

Influenza did not appear until 1403 and 1404, when it spread through Northwestern Europe. It began apparently in Paris, where nearly 100,000 were attacked and great prostration occurred. It extended into Flanders, the Netherlands and Northern Germany in 1404, according to Ripperger, who from his authority, Pasquier, concludes this to have been a true epidemic of the disease. The disease did not apparently completely disappear, for we read of its appearance in widespread form in Paris again in 1411, where it was spoken of as a "general contagion in the air." Chronicles at this period describe a more virulent form of disease accompanied at times with hemoptysis epistaxis, rectal hemorrhage and abortion in pregnant women. The malady continued to prevail during the ensuing years in France and Italy. It became widespread in January and February of 1414, according to Hirsch, who states that it was particularly prevalent in the great cities of Italy, and was attributed to "certain influences of the wind." At this time some confusion as to nomenclature arose. Though it was generally spoken of as "le tac," the French also spoke of it as "le coqueluche," a name that was also applied to pertussis.

In Creighton's "History of the Epidemics in Britain" there appears a quotation from an unknown source that describes the epidemic that prevailed in England in October of 1427. The malady had been propagated apparently from Paris, where it previously was rampant, and had occasioned great suffering. In England it was called "mure," and, as the description goes, "so infected the aged along with the younger, that it conducted a great number to the grave." From this time until 1510, no description of an epidemic can be found, though reference is made by several historians of mild outbreaks of the disease.

Influenza as it occurred in 1510 ushered in a new picture of the disease. Though it had hitherto been regarded as a more or less localized pestilence, burning out as it were after it had lasted a few months or visited a defined area, we now see it originating in Southeastern Europe, and spreading along definite lines over the entire continent. Whether this picture of a pandemic as the disease at once appears, developed through the accumulation of more accurate descriptions and correlated data, cannot be said. It seems strange that so highly contagious a disease did not flourish in greater waves before the beginning of the sixteenth century. One is more inclined to believe that at the threshold of modern times, a broader intercourse between nations, a tendency of one people to investigate affairs of its neighbor, and the commencement of commercial rivalries opened the avenues for greater international interest between peoples, and stimulated the study of experiences and recording of events in other countries. Thus we suddenly find numerous historians agreeing as to the character and the widespread tendency of the disease. One may find not only references in the several excellent histories on influenza, but anyone who has access to the older writers such as Fernelius, Johannes Schenk, Saillant, and Thomas Short will find accurate descriptions of the disease. From 1510 to 1511 the wave swept over from the region of the Grecian Archipelago into Italy, across the mountains into Slavic countries, into Germany, Hungary, France, Belgium, and the Netherlands, crossed to England and invaded Spain. During July and August it existed over a widespread area, striking down whole populations, though not causing any alarming mortality. There is described on the one hand, intense headache, cough, hoarseness, pain in back and legs, prostration and fever; on the other, instances of anorexia, vomiting, pains in stomach, with many cases of diarrhea and sweating. Both blisters and bleeding were employed in the treatment of the disease and considered of real service.

In 1557 another pandemic appeared. It originated in the same region as the previous one, spreading over the whole of Europe and England. It was of great virulence in some localities, for in Thompson's "Annals" and in Creighton appear reports of drunkards dying, pregnant women aborting and succumbing, and little children and the weakly falling victims to the disease. Apparently the pulmonary complications were many and severe, for physicians resorted early to counterirritation over the chest and sides, and practiced bleeding frequently. The disease prevailed from July to October as a widespread malady. It subsided for a while, only to flare up again in sporadic outbreaks in England in 1558 and 1562. Here it was called the "new acquayntance." Mary, Queen of Scots, as well as her entire court, fell victims to it. They all recovered promptly.

Probably one of the severest epidemics, both as to the number stricken, and the universal extent, occurred as the pandemic of 1580. Like previous "visitations" of this pestilence it originated in Southeastern Europe. One finds references to it in many general histories of the times, for it affected profoundly all the nations of the globe. It spread with astounding rapidity in every direction, invading simultaneously Western Asia, Northern Africa, and Southern Europe. Then it sprang eastward into the remote nations of the Orient, at the same time crossing the mountains of Europe and spreading through the oft-afflicted peoples of this territory. In fact it ravaged every section of the earth. Though no trustworthy record of it is discoverable, it must have prevailed on this continent. Literally, millions were stricken. Thousands died. It lasted for about six months (June to December) when it quickly abated. During this period the weekly death rate in London, when the disease was at its height, practically tripled itself. The usual symptoms were described. The more severe forms were ushered in with nervous symptoms, rigors or vomiting. Intense prostrations ensued. Bleeding was frequently resorted to, though the consensus of opinion of observers and chroniclers seems to be that venesection was attended with high mortality. Hirsch states that smaller epidemics followed this great pandemic of 1580 up to the close of the sixteenth century. Though the evidence is inconclusive, it is not unlikely from the historical evidence that Hirsch submits, that outbreaks took place in Italy, Germany and Western Europe.

It was not until 1626 that an outbreak in larger proportions is again recorded. The disease prevailed in Italy and Germany, whence it spread to Spain occurring there in quite violent form. Hirsch states that it was then recognized for the first time in America, though there is evidence that it also existed on the Western Hemisphere during the pandemic of 1557. Strange to say, the earliest definite mention of the disease in America is found in Noah Webster's "History of Epidemic Diseases" as taking place in 1647. He makes the interesting connotations: "Such as were bled or used cooling drinks died; such as made use of cordials or more strengthening things recovered."

A definite epidemic occurred in 1658. Willis, whose name is associated with the anatomical description of the "circle" of arteries at the base of the brain, says among other things in his description of this epidemic: "The third part of mankind almost was distempered within the space of one month," indicating quite accurately no doubt the morbidity of the disease and the rapidity of its attack.

Sporadic outbreaks are reported in 1675. Germany, Hungary, and parts of France suffered. Sydenham has written on this epidemic as it afflicted London, stating that hardly anyone was spared and that pleurisies and pneumonias were frequent complications. He also recorded a recrudescence of the disease in November of 1679, when the deaths from all causes in London more than doubled.

Molineux, of Dublin, gives a most graphic description of the epidemic of 1688. It was particularly in England and Ireland that the disease raged violently. He speaks of an onset "with a chilliness and shivering all over....and a dull pain in their heads chiefly about the eyes....and about the small of the back. Giddiness and lack of appetite would continue for some days afterwards, but with the use of open fresh air, they certainly, at farthest, recovered these likewise, and were perfectly well." Another interesting observation of Molineux which does not appear in the description of earlier epidemics is that old people, as a rule, were not susceptible and generally escaped the attack. This is at variance with previous chroniclers, but coincides with the general experience in our recent pandemic. The disease reappeared in Ireland and England in 1693 and spread to the Continent invading the Channel and North Sea countries.

Some doubt exists as to whether an epidemic existed in 1709 (Hirsch). However, in 1712 Southern and Central Europe were visited by influenza in a violent manner. The attacks as described by many writers did not differ from previous ones. There was great morbidity, but not high mortality.

The great pandemic that began in Russia in 1729 really lasted for three years. In that period of time it traveled over the face of the globe. In April it appeared in Russia, traveled rapidly westward, ravaged Poland and Sweden that fall, reached Western Europe and England that winter, then extended south, and in the following February was spread over Italy and Spain. It then subsided for awhile, occurring sporadically, to return again in 1732. It spread with violence in England. In Edinburgh, where it is first recorded in December, the mortality rate rose rapidly. Huxham, of Plymouth, in his "Essay on Fevers," speaks of its passage into "bastard pleurisy and peripneumony." When the disease attacked London over 500 died in one week. In that same year the epidemic swept the seaboard of the Atlantic in North America and later passed through the West Indies, Mexico, and South America. In addition to the respiratory complaints, Webster records the marked nervous and gastro-intestinal symptoms that were observed.

During these years this disease had not been distinguished by a definite term. It was known frequently in England as "the new disease," "the new acquayntance," "the new ague," and "the new burning ague." In France "Le coqueluche" was used most commonly, though "toux catarre" and "la baraquette" were frequently names given to the disease. In Italy "una influenza de freddo" (an influence of cold) had been used for many years. From this the term influenza originated. The designation was developed by the English in 1743, and particularly by Sir John Pringle, Surgeon General of the English Army from 1742 to 1758. This noted military surgeon during this period instituted numerous far-reaching reforms in army sanitation and medical military tactics, and wrote several useful treatises on acute infectious fevers raging in the army. He was able to speak authoritatively on influenza, for he witnessed the epidemics of 1742 and 1743, as well as several minor outbreaks, the last of which occurred in 1758. Though the term influenza was in general use, it was not until 1782, the year of Pringle's death, that the Royal College of Physicians of London formally accepted it. The French also during this epidemic sought to name the disease definitely. "La Grippe" then originated, it coming gradually from the verb "agripper" (to seize). Hence the words influenza and la grippe, which up to the present time have been used synonymously, were evolved at about the same period. This epidemic of 1742, like several previous ones, began in Russia and moved from east to west. Great numbers were stricken. Though accounts are fragmentary, Pringle speaks of its affecting the soldiers. Bloodletting was freely practiced. It was looked on with some favor in England; from Italy came reports that many died from the "use of the lancet."

The years of 1761 and 1762 found a return of the disease throughout the world. It raged from March through May in the New England States. During the following year it covered Europe, appearing first in Germany in February, and gradually following the lines of travel, later invading Ireland, Scotland, France, Poland and cities along the Mediterranean Sea. Thirteen years later another epidemic ensued, lasting from March, 1775, to January, 1776. It traveled through Central and Western Europe and the British Isles, causing no great mortality. During the next few years several accounts exist of sporadic occurrences. Nothing new is recorded in regard to the symptomatology or epidemiology, except that Fothergill of London conducted an inquiry among physicians in regard to the contagiousness of influenza. Naturally there was great variation of opinion expressed as to the cause. Yet it is surprising to see how many inclined toward the conception of the contagious nature of the disease.

In 1781 and 1782 one of the greatest of all pandemics is recorded. In September of 1781 it originated in the far East, probably in India. Many British soldiers were stricken. Spreading northward and eastward into China and westward along lines of communication, it reached Siberia and Russia early in 1782. The pestilence decimated the cities of Petrograd and Moscow, traveling through the Scandinavian countries and into Poland in March and April of 1782. Then it reached southward, progressing through Germany in April, May and June, and extending simultaneously to the British Isles and along the Atlantic coast in the Netherlands and France. The next months found it in Italy, and in August it had reached Spain. So acute was the onset in many instances that one English physician (Gregory) speaks of people being stricken and falling in the streets,—not unlike some observations in our recent epidemic. Though previous reports exist of the disease occurring on shipboard, the Transactions of the Royal College of Physicians at this time makes mention of the disease breaking out on shipboard among the sailors of the English fleet while on the high seas. A great many descriptions of the disease as it prevailed are at hand. They add nothing to earlier expositions of the signs, symptoms, and complications. A few facts are of noteworthy interest. In some of the larger cities over a thousand became ill in one day. In Vienna the theaters were closed for eight days. The total death rate, where compilations were made, tripled for a few weeks during the height of the epidemic.

In 1789 influenza was widespread in the United States of America. It had existed during the previous year in Europe, so it is highly probable with the distance between continents and the paucity of travel, that some time elapsed before it was definitely transported to this country. It spread with great rapidity. Appearing in September in New York and Philadelphia, it reached Massachusetts by November, invading all the New England States and Canada during the winter. At the same time it traveled, as it had previously done, into the West Indies and South America.

This brings us to the beginning of the nineteenth century, during which influenza ravaged the earth on several occasions. Though the disease did not occur more frequently in great waves, sporadic outbreaks and small epidemics were successively recorded. And what is particularly noteworthy was the tendency of the disease to break out for successive years in neighboring localities. Greater facilities for travel, and broader commercial intercourse made for greater intermingling of individuals and wider dissemination of the virus, especially through susceptible individuals.

If one reviews the history of the disease from the beginning of the nineteenth century, it becomes at once apparent that scarcely a year passes without some reappearance of influenza. Franklin writes of the epidemic of 1802-1803 that it "made its appearance during the winter of 1802 in France, although the disease had prevailed during the last three months in 1800, and in the beginning of the year, 1801, in Germany and France as well as in China and Brazil.''

In the first decade of the nineteenth century we find innumerable descriptions of influenza. A decided unanimity of opinion seems to exist in reference to the prevalent symptomatology. English authors speak of marked prostrations that occurred, of the similarity of some of the cases to typhoid fever and of the severe sequelæ that were sometimes seen. In this country influenza spread quite generally throughout the east, and later extended into the newly developed districts in our midwestern states. It was not confined to the cities, but apparently attacked the rugged and healthy in the rural districts, playing havoc for a while among the Indians. In the second decade we find that the United States again felt the ravages of the disease, for in 1816 an epidemic that seemed especially fatal to children, who succumbed quickly to it, was rather widespread. At this time it was more prevalent in the southeastern section of this country. In the middle of the third decade we find records of a wave passing across this continent. It was in Pennsylvania in September, in Massachusetts and New York in October. Thence it quickly visited the states along the southern and eastern section of this country, traveling from there into the West, into Mexico and finally into South America.

During the next twenty years there were really two great pandemics. The first running from 1830 well into 1833. The second from 1847 to 1849. In the interim the disease appeared as sporadic outbreaks that might well be called individual epidemics, for it flourished in nearly every intervening year in some part of the globe. Of the former pandemic, it can be safely said that it originated in the Phillippine Islands, whence it spread to China by the end of 1830. Early in the following year it was prevalent in Russia. At the same time it had traveled eastward from the Philippines, visiting the South Sea Islands, where many of the natives were stricken with the disease. From Russia it traveled as it had previously done in other epidemics, through Scandinavia and Poland into Germany, quickly finding its way into France, Belgium, Spain and Italy. It took about three months for it to appear on this continent. Not until it had entirely encircled the globe, did its onward march subside. This in all took about three years. Scarcely was there a country that it did not invade. All historians agree that the ravages of this disease in the years of 1830, 1831 and 1833, which many describe as individual epidemics, gave rise to an unprecedented morbidity. There was great destruction of life in some regions during 1833. In London during the four weeks from April 24th to May 21st, 3,350 deaths are recorded, many of the fatalities being among the better classes. From various descriptions one gathers the fact that the disease came on suddenly with intolerable headache, high temperature and respiratory symptoms. Bleeding was much practiced at this time, though previous experience had contraindicated it. It afforded little or no relief. The conception of the contagiousness of the disease made no headway, chiefly because of the simultaneous occurrence of the disease in several places, and the rapidity with which it subsided.

The severe pandemic that ravaged the European continent from 1847 through 1848 is chiefly of interest because of the unusual increase in mortality rate that is recorded at this time. American physicians especially, through the influence of the French school of clinical teachers, came to recognize more and more that the complications, particularly of pneumonia, were the dangerous features of the disease. Just previously the French had pointed out that the pneumonia following influenza differed from the ordinary croupous pneumonia in many respects. They spoke of its gradual onset during influenza, of physical signs of a fine bronchitis, of the absence of dulness until late in the disease, and the delayed appearance of bronchial breathing. During this epidemic those who had suffered previous disease of the respiratory tract were often fatally stricken. Children, too, at this time frequently succumbed to the disease. The death rate from influenza and nontuberculous respiratory disease had been about 90 per 100,000. During this period it rose to 240 per 100,000. Statistics of London for 1847-1848 are of interest:

Age	*Incidence of Influenza per 100,000 People.*
Under 1	154.0
1-9	88.0
10-19	4.0
20-29	6.5
30-49	50.8
50-69	140.0
70 and over	1,084.5

From 1850 until the great pandemic of 1889-90, there were really two major epidemics of influenza. During these 40 years records are at hand describing many lesser outbreaks of influenza in every part of the world. At times flaring up in proportions of an epidemic, the disease would apparently burn itself out, after having spread over a considerable area. There was scarcely a year that it did not appear in some region. The outbursts of the disease in 1850-51, in 1857-58 and in 1873-1875 affected both hemispheres. Particularly prevalent was the disease in this country in 1873. It was not until 1889-90 that a pandemic of real proportions passed over the earth. Like other great flares of influenza, it burst forth in the far East. Occurring at a time in human history when the modes of transportation had rapidly reached a high state of development, the rate of diffusion was more rapid than during any previous pandemic. It was in fact quite proportionate to the rate of human travel. It undoubtedly began in May, 1889, in Bokhara. In October it was prevalent in Siberia and Russia, especially in Petrograd. It overran this city rapidly. Once reaching a large center of population and commercial activities with its innumerable lines of communication, the disease was quickly diffused in every direction. The surrounding country soon suffered. At the same time railroad routes carried influenza to the great cities of Sweden, Denmark, and Germany. This was toward the first of December. Three weeks later all Europe was completely infested. In fact the disease crossed the Atlantic at this time, cases being reported in New York about December 20. The British Isles were attacked at the same time. Three months after it had appeared in Russia, epidemics prevailed in such widely separated countries as Japan, Capetown, Hawaii and Mexico. In ten months it had spread its desolation into every land and every climate, sparing but few, and establishing foci where the disease had never before existed. It subsided in each locality in from six weeks to two months, though in some areas it returned again during the following years. This feature of the disease is not uncommon, especially in the larger centers, where the population is constantly shifting, and individuals changing their abodes. In the United States the disease broke out in San Francisco, Boston, New York and Philadelphia almost at the same time. Each focus was probably independent of the other. The avenue of ingress was by steamship, though the infection on the western coast must have come by way of the Pacific, while the infection on the eastern coast may have traveled over several routes. All types of the disease prevailed in the United States. There was a great tendency, however, to the development of nervous symptoms, and of signs of marked prostration. Pulmonary complications caused many deaths. The death rates in a few of the principal cities of the world indicates the virulence of the epidemic.

Epidemic of 1889-90.

	Average Annual Death Rate per 1,000 Previous to Epidemic.	*Average Death Rate at Peak of Epidemic.*
London	20	32.3
Paris	26.3	60.8
Berlin	19.9	36.8
St. Petersburg	22.2	39.5
New York	21.6	44.9
Boston	22	48.3

As will be seen later the mortality rate was much less than in the last epidemic. Many accurate reports of this epidemic are available. Health Board reports from various states and municipalities in the United States as well as from foreign sources all bear witness to the universality of the epidemic, its general characteristics and the mortality rate. This varied, of course, in different parts of the world. Generally, however, the average rate of mortality from all sources did not increase more than twice the annual death rate from all sources during the height of the epidemic. In all instances the disease came on with a rush, reached the acme and subsided within six weeks. It was also pointed out during this period that the disease, though disseminated over wide areas, attacked far greater numbers of those whose work brought them in close contact with others; while those, who had out-of-door occupations, which they individually pursued, were less frequently attacked. For example, the class of railway laborers in a certain district in Germany suffered a morbidity of 8 per cent., whereas of the office and station employees in the same district 62 per cent. were attacked. The epidemic of 1889-90

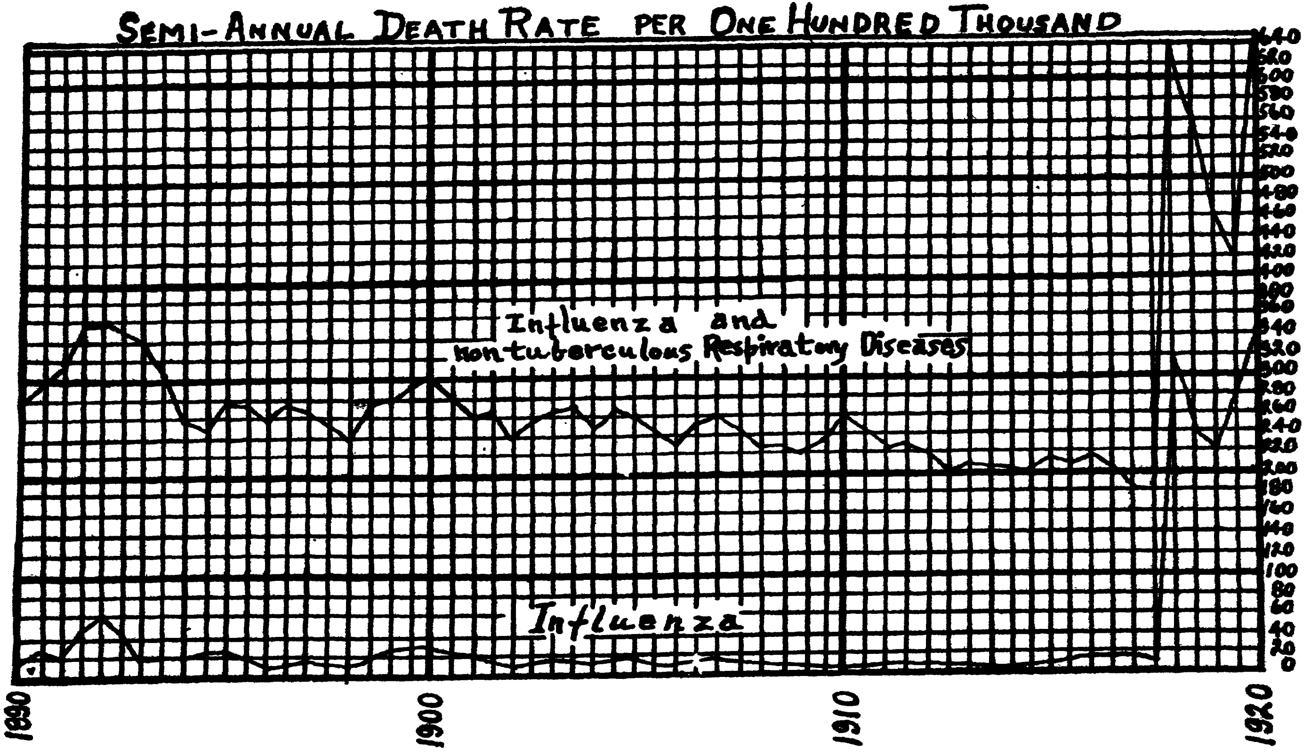
SEMI-ANNUAL DEATH RATE PER ONE HUNDRED THOUSAND
Influenza and nontuberculous Respiratory Diseases
Influenza
640
620
600
580
560
540
520
500
480
460
440
420
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
1890
1900
1910
1920

CHART V

differed from previous ones also in that young children escaped. Under the age of ten, the incidence was much less than in those over that age. Babies were rarely affected. The greatest incidence was between ten and thirty years of age.

Following the pandemic of 1889-90, several mild epidemics occurred. During December and January of 1893-1894 the disease flourished in England, though it never became widespread. The annual death rate from influenza and nontuberculous respiratory diseases per 1,000 rose from 1.8 to 11.7. Sporadic outbreaks are recorded in this country: *viz,* one in Plattsburg Barracks (Surgeon General's Report of United States Army for 1896); one in 1895 and again in 1901 in New York City, where it recurred in mild form in the winter of 1907-1908 and in 1915-1916. It was in 1916 that the disease was rather widespread in the United States, though it at no time assumed epidemic proportions. This is noticeable in the increase of the death rate from nontuberculous respiratory diseases.

Chart No. V. indicates very well the incidence of the diseases since the pandemic of 1889-1890. It is taken from various tables and statistics and represents the average annual death rate from influenza, as well as from influenza and all other respiratory diseases.

BIBLIOGRAPHY

ABT, I. A. Influenza in a newly-born infant: Report of a case. Jour. Amer. Med. Assoc., 1919, lxxii, 980.

ABT, I. A., AND TUMPEER, I. H. Influenzal meningitis with report of a case. Amer. Jour. Dis. Child., 1921, xxi, 444.

ALEXANDER, M. E., AND MACDONALD, E. L. Observations on the latest (1920) recrudescence of influenza. Amer. Jour. Med. Sci., 1920, clx, 674.

ARMBRUSTER. Surgery in influenza. Arch. Diag., 1917, x, 69.

AVERY, O. N. Bacillus influenzæ: A selective medium for oleate-hemoglobin agar. Jour. Amer. Med. Assoc., 1918, lxxi, 2050.

BAKWIN, H. Gross pathology of influenzal pneumonia. Amer. Jour. Med. Sci., 1920, clix, No. 576, p. 435.

——— Gross pathology of influenzal pneumonia in France. Amer. Jour. Med. Sci., clix, 435.

BEHREND, M. Acute appendicitis complicating epidemic influenza, with report of 8 cases. Surg., Gyn. & Obstet., 1919, xxviii, 601.

BELL, H. H. Relation of different strains of influenza bacilli. Jour. Infec. Dis., 1920, xxvii, 464.

BIELONG AND WEICHBRODT. Serologische untersuchungen bei Grippe und Encephalitis epidemica. Deut. Mediz. Wchnschr., 1920, Jahrgang xlvi, 1183.

BLACKWELL, H. B. Perisinus and epidural mastoid abscess subsequent to influenza. Arch. Diag., 1919-20, xii, 47.

BLAKE AND CECIL. Production of an acute respiratory disease in monkeys by inoculation with bacillus influenzæ. Jour. Amer. Med. Assoc., 1920, lxxiv, 170.

BLANTON AND EISENDRATH. Abdominal complications of the influenza epidemic at Camp Custer. Jour. Amer. Med. Assoc., 1919, lxii, 850.

BLOOMFIELD, A. L. The fate of influenza bacilli introduced into the upper air passages. Bull. Johns Hopkins Hosp., 1920, xxxi, 85.

BLOOMFIELD AND HARROP. Clinical observations on influenza epidemic. Bull. Johns Hopkins Hosp., 1919, xxx, 1.

Bloomfield and Mateer. Changes in skin sensitiveness to tuberculin during epidemic. Bull. Johns Hopkins Hosp., 1919, xxx, 238.

Bloomfield, A. L., and Waters, C. A. Correlation of x-ray findings and physical signs in the chest in uncomplicated epidemic influenza. Bull. Johns Hopkins Hosp., 1919, xxx, 252.

Bradbury, S. Influenza epidemic in soldiers. Amer. Jour. Med. Sci., 1918, clvi, 737.

Bradbury and Krumbhaar. Influenza at a Base Hospital in France. Arch. Diag., 1919-20, xii, 45.

Brem, Bolling and Casper. Pandemic influenza and secondary pneumonia at Camp Fremont, California. Jour. Amer. Med. Assoc., 1918, lxxxi, 2138.

Brewster, I. W. Report of epidemic of "Spanish influenza" which occurred at Camp A. A. Humphreys, Va. Jour. Lab. & Clin. Med., 1918-19, iv, 87.

British Medical Research Committee, Abstracts of foreign literature compiled by. Jour. Amer. Med. Assoc., 1918, lxxi, 1573.

Bugbee, H. G. Infections of the genito-urinary tract complicating influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 1053.

Bunting, C. H. Leukokytic picture in influenza. Amer. Jour. Med. Sci., 1921, clxii, 1.

Burr, C. W. Influenza in a case of specific meningomyelitis with cystitis. Arch. Neur. & Psych., 1920, iii, 536.

Caffrey, A. J. Quinin in influenzal pneumonia. Jour. Amer. Med. Assoc., 1920, lxxiv, 1166.

Calderon, F. Influence of influenza on menstruation, pregnancy and puerperium. Jour. Amer. Med. Assoc., 1919, lxxiii, 982.

Catsaras, J. Embolies graisseuses pulmonaries dans la bronchopneumonie grippale. La Presse méd., 1920, xxviii, 618.

Christian, H, A. Incorrectness of the diagnosis of death from influenza: Presence of bronchopneumonia in practically all persons severely ill with influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1565.

Clark, E., and Synnott, M. Influenza-pneumonia cases showing gas in fascial tissues. Amer. Jour. Med. Sci., 1919, clvii, 219.

Clark, L. P. Influenza and epileptiform attacks. Jour. Amer. Med. Assoc., 1919, lxxiii, 1767.

Conner, H. L. Incidence of streptococcus hemolyticus in a recent epidemic. Jour. Lab. and Clin. Med., 1920, v, 767.

Conner, L. A. Symptomatology and complications of influenza. Jour. Amer. Med. Assoc., 1919, lxxxiii, 321.

Cooke, J. V. Complement fixation in influenza with bacillus influenza antigens. Jour. Infec. Dis., 1920, xxvii, 476.

Coskinas, G. S. Sur les epanchements aseptiques pneumogènes de la plèure consecutifs aux lésions pulmonaires grippales. La Presse méd., 1920, xxviii, 43.

Coutant, A. F. An epidemic of influenza at Manilla, P. I. Jour. Amer. Med. Assoc., 1918, lxxi, 1566.

Cowie and Bevan. On the clinical evidence of involvement of the suprarenal glands in influenza and influenzal pneumonia. Arch. Int. Med., 1919, xxiv, 78.

——— Non-specific therapy in influenza. A consideration of the action of typhoid protein. Jour. Amer. Med. Assoc., 1919, lxxii, 1117.

Crowe and Thacker-NeVille. Influenza bacillus in paranasal sinus infections. Bull. Johns Hopkins Hosp., 1919, xxx, 322.

Current Comment. Value of vaccination against influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1583.

——— Influenza and tuberculosis. Jour. Amer. Med. Assoc., 1919, lxxiii, 1942.

——— Three early epidemics of influenza. Jour. Amer. Med. Assoc., 1920, lxxiv, 606.

——— Cyanosis in influenza. Jour. Amer. Med. Assoc., 1919, lxxii, 1619.

——— The epidemic of influenza. Jour. Amer. Med. Assoc., 1919, lxxi, 1063.

——— No specific cure for influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1489.

Dick, G. H. and Murray, E. Observations on the bacteriology of influenza. Jour. Infec. Dis., 1919, xxv, 6.

Dick and Murray. The morphology of the bacillus. Jour. Amer. Med. Assoc., 1918, lxxi, 1568.

Discussion. Influenza. Brit. Med. Jour., 1920, i, 191.

——— Proper course for physician and patient. Jour. Amer. Med. Assoc., 1920, lxxiv, 328.

Douglas, B. Reaction of the leukocytes in influenza epidemic. Bull. Johns Hopkins Hosp., 1919, xxx, 338.

Duval and Harris. Rôle of the Pfeiffer bacillus. Jour. Infec. Dis., 1919, xxv, 384.

——— Antigenic property of the Pfeiffer bacillus. Jour. Immun., 1919, iv, 317.

Edgerly, E. T., Manson, F. M., Divinell, W. G., and Carr, J. G. Influenza-pneumonia epidemic at Camp Dodge. Amer. Jour. Med. Sci., 1919, clviii, 212.

Edington, J. W. An investigation into the causal organism of influenza. Lancet, 1920, ii, 340.

Editorial. Influenza in Germany. Jour. Lab. and Clin. Med., 1918-1919, iv, 142.

——— Quarantine and isolation in influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1220.

Recent observations on influenza in Germany. Jour. Amer. Med. Assoc., 1919, lxxii, 1466.

——— "Spanish influenza." Jour. Amer. Med. Assoc., 1918, lxxi, 660.

——— Influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 1064.

Etiology of influenza. Various views of identity and causation of outbreaks. Jour. Amer. Med. Assoc., 1919, lxxii, 1000.

Egbert, W. F. Postinfluenzal psychoses. Jour. Amer. Med. Assoc., 1919, lxxii, 1658.

Evans, W. A. Report of a special committee of the American Public Health Association. Jour. Amer. Med. Assoc., 1918, lxxi, 2068.

Fantus, B. Clinical observations on influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1736.

Fell, E. W. Influenzal psychoses. Arch. Diag., 1919-20, xii, 45.

Ferry and Houghton. Some suggestive experiments with bacillus influenzæ. Its toxin and antitoxin. Preliminary report. Jour. Immun., 1919, iv, 233.

Fischer. Zur klinik der epidemischen Grippe im Säuglingsalter. Deut. Mediz. Wchnschr., 1920, xlvi, S. 75.

Fishberg, M. Influenza in the tuberculosis. Amer. Jour. Med. Sci., 1920, clx, 214.

Forbes and Snyder. Study of the leukocytes in an epidemic of influenza. Jour. Lab. and Clin. Med., 1917-18, iii, 758.

——— Study of leukocytes in influenza. Arch. Diag., 1918, xi, 140.

Fraenkel, E. Eye complications. Deut. Mediz. Wchnschr., 1920, xlvi, 673.

———Ueber Augenerkrankunger bei Grippe. Deut. Mediz. Wchnschr., 1920, xlvi, 1182.

Frick, D. J. Review of the epidemic of influenza at the base hospital, Camp Beauregard. Amer. Jour. Med. Sci., 1919, clviii, 68.

Friedemann, U. Therapeutische Erfahrungen aus der diesjährgen Grippe epidemic. Deut. Mediz. Wchnschr., 1920, xlvi, S. 283.

Friedlander, McCord, Sladen and Wheeler. The epidemic of influenza at Camp Sherman, Ohio. Jour. Amer. Med. Assoc., 1918, lxxi, 1652.

Frost, W. H. Epidemiology of influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 313.

Frothingham, C. Influenza. Amer. Jour. Med. Sci., 1921, clxi, 528.

Fry, H. J. B. Complement-fixation experiments in influenza. Lancet, 1920, i, 368.

Gay, F. P. Present status of our knowledge concerning the etiology of influenza. Jour. Lab. and Clin. Med., 1919-20, v, 543.

Gay and Harris. Serum reactions in influenza. Jour. Infec. Dis., 1919, xxv, 414.

Goodpasture, E. W. Significance of certain pulmonary lesions in relation to the etiology of influenza. Amer. Jour. Med. Sci., 1919, clviii, 863.

Gordon, A. Mental disorders following influenza. Arch. Int. Med., 1919, xxiv, 633.

Gram, F. C. Influenza epidemic and its after-effects in the city of Buffalo. Jour. Amer. Med. Assoc., 1919, lxxiii, 886.

Hall, M. W. Study of the lesions produced by filtrates influenza sputum. Arch. Int. Med., 1920, xxvi, 612.

Hamilton and Leonard. Acquired immunity to influenza as indicated by a recurrent epidemic in an institution. Jour. Amer. Med. Assoc., 1919, lxxii, 854.

Harris, J. W. Influenza occurring in pregnant women. A statistical study of 1350 cases. Jour. Amer. Med. Assoc., 1919, lxxii, 978.

Harrop, G. A., Jr. The infections. The behavior of the blood toward oxygen. Bull. Johns Hopkins Hosp., 1920, xxx, 10.

Hazen, H. H. Postinfluenzal alopecia. Jour. Amer. Med. Assoc., 1919, lxxii, 1452.

Hewlett and Ablerty. Influenza at a navy base hospital in France. Jour. Amer. Med. Assoc., 1918, lxxi, 1056.

Hirsh and McKinney. Further studies in influenza epidemic at Camp Grant. Jour. Infec. Dis., 1919, xxv, 394.

Honeij, J. A. Influenza pneumonia; certain radiological features of the disease in the epidemic of 1920. Amer. Jour. Med. Sci., 1920, clx, 669.

Howard, S. E. Bacteriological findings in epidemic. Bull. Johns Hopkins Hosp., 1919, xxx, 13.

Howell and Anderson. Complement-fixation in influenza. Jour. Infec. Dis., 1919, xxv, 1.

Huntoom and Hannum. Rôle of bacillus influenzæ in clinical influenza. Jour. Immun., 1919, iv, 167.

Johnson, C. K. A case of influenzal meningitis. Arch. Ped., 1919, xxxvi, 82.

Jordan, E. O. Production of indol by certain strains of the Pfeiffer bacillus. Jour. Amer. Med. Assoc., 1919, lxxii, 1542.

——— Influenza in three Chicago groups. Jour. Infec. Dis., 1919, xxv, 74.

Jordan, E. O., and Sharp, W. B. Influenza studies. I. Immunity in influenza. Jour. Infec. Dis., 1920, xxviii, 463.

——— Influenza studies. IV. Effect of vaccination against influenza and some other respiratory infections. Jour. Infec. Dis., 1920, xxviii, 357.

Keegan, J. J. The prevailing pandemic of influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1051.

Keeton, R. W., and Cushman, A. B. The disease as a type of toxemic shock. Jour. Amer. Med. Assoc., 1918, lxxi, 1962.

——— Influenza epidemic in Chicago. Arch. Diag., 1918, xi, 215.

Kerr, Berkley and Coffen. Influenza and bronchopneumonia at Camp Lewis. Arch. Diag., 1919-20, xii, 115.

Kinnicutt and Binger. Isolation of the meningococcus from cases of so-called influenza. Amer. Jour. Med. Sci., 1919, clviii, 360.

Kinsella, R. A. Bacteriology of influenza and pneumonia epidemic. Arch. Diag., 1918, xi, 289.

Kinsella, R. A., and Broun, G. O. Changes in the blood in influenza. Jour. Amer. Med. Assoc., 1920, lxxiv, 1070.

Kolmer, Trist and Yagle. Serum studies on the etiology of influenza. Jour. Infec. Dis., 1919, xxiv, 583.

Kotz, A. L. Influenza and bronchopneumonia at the Easton Hospital, Easton, Pa. Jour. Lab. and Clin. Med., 1918-19, iv, 424.

Kraus, F. Zur Behandlung der Grippe. Deut. Mediz. Wchnschr., 1920, xlvi, S. 225.

Lacy, G. R. Bacillus influenzæ in sinusitis and meningitis. Jour. Lab. and Clin. Med., 1918-19, iv, 55.

LaFetra, L. E. Some clinical manifestations of influenza in children. Amer. Jour. Med. Sci., 1919, clvii, 770.

Lamb, F. H., and Brannin, E. B. Epidemic respiratory infection at Camp Cody. Jour. Amer. Med. Assoc., 1919, lxxii, 1056.

LeCount, E. R. Pathologic anatomy of influenzal bronchopneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 650.

——— Disseminated necrosis of the pulmonary capillaries in influenzal pneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 1519.

Leishman, Sir Wm. B. The results of protective inoculation against influenza in the army at home. Lancet, 1920, i, 366.

——— The results of protective inoculation against influenza. Brit. Med. Jour., 1920, i, 214.

Levin, Goodman and Pancoast. Relation of the streptococcus hemolyticus to influenza and pneumonia. Amer. Jour. Sci., 1919, clviii, 202.

Levin. Influenza and its complications in children. Internat. Clin., 1920, Series xxx, ii, 64.

Levinson, A. Clinical observations on influenza, with special reference to the blood and blood-pressure. Jour. Infec. Dis., 1919, xxv, 18.

Loewe, L., and Zeman, F. D. Cultivation of a filtrable organism from the nasopharyngeal washings in influenza. Jour. Amer. Med. Assoc., 1921, lxxvi, 986.

Loewenhardt, E. R. Bakteriologische Befunde bei Influenza. Deut. Mediz. Wchnschr., 1920, xlvi, S. 794.

Longcope, W. T. Survey of the epidemic of influenza in the American Expeditionary Forces. Jour. Amer. Med. Assoc., 1919, lxxiii, 189.

Lucke and Barker. Cytological studies of pleural exudates complicating influenza. Amer. Jour. Med. Sci., 1919, clviii, 577.

Lucke, Wight and Kime. Pathologic anatomy and bacteriology of influenza; epidemic of autumn, 1918. Arch. Int. Med., 1919, xxiv, 154.

Lynah, H. L. Influenzal croup. Amer. Jour. Dis. Child., 1919, xviii, 238.

Lynch and Cumming. Epidemiology of influenza-pneumonia. Jour. Lab. and Clin. Med., 1919-1920, v, 364.

Lyon, Tenney and Szerlip. Some clinical observations on the epidemic at Camp Upton. Jour. Amer. Med. Assoc., 1919, lxxii, 1726.

——— Some clinical observations on influenza epidemic at Camp Upton. Arch. Diag., 1919-20, xii, 42.

McClelland, J. E. Bacteriological observations on the epidemic of influenza at Camp Beauregard. Amer. Jour. Med. Sci., 1919, clviii, 80.

McConnell, G. Blood-picture of those inoculated with influenza vaccine. Jour. Amer. Med. Assoc., 1919, lxxii, 1457.

——— The relation of influenza bacillus to the recent epidemic. Amer. Jour. Med. Sci., 1919, clviii, 47.

McCord, Sladen, and Wheeler. Epidemic at Camp Sheridan. Arch. Diag., 1918, xi, 115.

McCoy, G. W. Status of prophylactic vaccination against influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 401.

McGlannan, A. Some abdominal complications of influenza. Surg., Gyn. and Obstet., 1920, xxx, 462.

McGuire and Redden. Treatment of influenza-pneumonia by the use of convalescent human serum. Jour. Amer. Med. Assoc., 1918, lxxi, 1311.

Macklin, A. H. Influenza amongst the Lapps. Brit. Med. Jour., 1920, i, 465.

Maclachlan and Feter. Citrated blood in treatment of the pneumonia following influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 2053.

MacNeal, W. J. Influenza epidemic of 1918 in the American Expeditionary Forces in France and England. Arch. Int. Med., 1919, xxiii, 657.

Manson, F. M. Report of the Surgical Service, U. S. Army Base Hospital, Camp Dodge. Amer. Jour. Med. Sci., 1919, clviii, 244.

Matz, P. B. Influenza at Camp Travis, Texas. Amer. Jour. Med. Sci., 1919, clviii, 723.

Meader, Means and Hopkins. Influenza among American troops in England. Amer. Jour. Med. Sci., 1919, clviii, 370.

Menninger, K. A. Further studies upon the relations of mental diseases and influenza. Amer. Jour. Med. Sci., 1921, clxi, 884.

——— Psychoses associated with influenza. Arch. Diag., 1918, xi, 219.

——— Interrelation of an acute epidemic infection and chronic endemic affection. Jour. Amer. Med. Assoc., 1920, lxxv, 1044.

——— Influenza and neurosyphilis. Arch. Int. Med., 1919, xxiv, 98.

——— Influenza psychoses in successive epidemics. Arch. Neur. and Psy., 1920, iii, 57.

Minaker and Irvine. Prophylactic use of mixed vaccine against pandemic influenza and its complications. Jour. Amer. Med. Assoc., 1919, lxxii, 847.

Moffett, R. D. Review of the literature on influenza in children. Arch. Ped., 1919, xxxvi, 578.

Montgomery and Dunham. Leukocyte counts during influenza in infants. Amer. Jour. Dis. Child., 1919, xviii, 153.

Morrissey, M. J. Influenza alopecia. Jour. Cut. Dis., 1919, xxxvii, 177.

Muller, E. F. Aspergillus fumigatus in the lungs in influenza. Deut. Mediz. Wchnschr., 1920, xlvi, 1169.

Neal, J. B. Influenzal meningitis. Arch. Ped., 1921, xxxviii, 1.

Nicolle, C., et Lebailly, C. Recherches experimentales sur la grippe. Annales de l'Institut Pasteur, 1919, xxxiii, 395.

Nuzum, Pilot and Stangl. Pandemic influenza and pneumonia in a large civil hospital. Jour. Amer. Med. Assoc., 1918, lxxi, 1562.

Olitsky and Gates. Experimental studies of the nasopharyngeal secretions from influenza patients. Jour. Exper. Med., 1921, xxxiii, 125.

——— Studies of the nasopharyngeal secretions from influenza. Jour. Amer. Med. Assoc., 1921, lxxvi, 640.

——— Experimental study of the nasopharyngeal secretions from influenza patients. Jour. Amer. Med. Assoc., 1920, lxxiv, 1497.

Park, W. H. Bacteriology of recent pandemic of influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 476.

Parker, J. T. A filtrable poison produced by bacillus in influenza. Jour. Amer. Med. Assoc., 1919, lxxviii, 476.

——— Poisons of influenza bacillus. Jour. Immun., 1919, iv, 331.

Pollard, R. The control of influenza. Brit. Med. Jour., 1920, i, 258.

Pritchett, I. W., and Stillman, E. G. Occurrence of bacillus influenzæ in throats and saliva. Jour. Exper. Med., 1919, xxix, 259.

Rackemann and Brock. Influenza at Camp Merritt, New Jersey. Arch. Int. Med., 1919, xxiii, 582.

Radin, M. J. Chronic lung disease following influenza. Amer. Jour. Med. Sci., 1920, clx, 233.

Rappoport, F. H. Complement-fixation test in influenzal pneumonia. Studies with serum from convalescent patients, the influenza bacillus being used as antigen. Jour. Amer. Med. Assoc., 1919, lxxii, 633.

Richter, C. M. Influenza pandemics depend on certain anticyclonic weather conditions for their development. Arch. Int. Med., 1920, xxvii, 361.

RIVERS, T. M. Effect of different bloods on the growth of bacillus influenzæ. Arch. Diag., 1919-1920, xii, 45.

——— Biological classification of influenza bacilli. Bull. Johns Hopkins Hosp., 1920, xxxi, 50.

ROBERTSON, H. E. Influenzal sinus disease in epidemic influenza. Jour. Amer. Med. Assoc., 1918, lxx, 1533.

ROOS, C. Notes on the bacteriology, and on the selective action of bacillus influenzæ Pfeiffer. Jour. Immun., 1919, iv, 189.

ROSENAU, M. J. Experiments to determine mode of spread of influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 311.

ROSENOW, E. C. Prophylactic inoculation against respiratory infections during the present pandemic of influenza. Jour. Amer. Med. Assoc., 1919, lxxii, 31.

——— XI. Therapeutic effects of a monovalent antistreptococcus serum in influenza and influenzal pneumonia. Jour. Infec. Dis., 1920, xxvi, 614.

——— Immunologic properties of the green-producing streptococci from influenza. Jour. Infec. Dis., 1920, xxvi, 597.

——— VIII. Experiments of the etiology of "gastro-intestinal" influenza. Jour. Infec. Dis., 1920, xxvi, 557.

——— VII. Study of the effects following the injection of bacteria found in influenza in normal throats in simple nasopharyngitis and in lobar pneumonia. Jour. Infec. Dis., 1920, xxvi, 504.

——— VI. Leukocytic reaction in influenza and pneumonia. Jour. Infec. Dis., 1920, xxvi, 492.

——— Studies in influenza and pneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 1604.

——— Studies in influenza and pneumonia. Jour. Infec. Dis., 1920, xxvi, 469.

——— IX. Changes in the green-producing streptococcus induced by successive animal passage and their significance in epidemic influenza. Jour. Infec. Dis., 1920, xxvi, 567.

ROSENOW AND STURDIVANT. Studies in influenza and pneumonia. IV. Further results of prophylactic inoculation. Jour. Amer. Med. Assoc., 1919, lxxiii, 396.

ROSS AND HUND. Treatment of the pneumonic disturbance complicating influenza. Jour. Amer. Med. Assoc., 1919, lxxii, 640.

RUSSELL AND STEFFEN. Acute respiratory infection in man following inoculation with virulent bacillus influenzæ. Jour. Infec. Dis., 1921, xxviii, 201.

SAELHOF, C. O. Influenzal pneumonia, correlation of rabbit pneumonia and human. Jour. Infec. Dis., 1921, xxviii, 374.

SANDY, W. C. Association of neuropsychiatric conditions with influenza. Arch. Neur. and Psychiat., 1920, iv, 171.

SCHMIDT, P. Zur Aetiologie von Schnupfen und Grippe. Deut. Mediz., Wchnschr., 1920, xlvi, 1181.

SCHOFIELD, F. W. Influenza in Korea, with special reference to its etiology. Jour. Amer. Med. Assoc., 1919, lxxii, 981.

SCHOTTEN, F. Interstitielles emphysem bei grippe. Deut. Mediz. Wchnschr., 1920, xlvi, S. 741.

SHERWOOD, N. P., DOROUS, C. M., AND MCNAUGHT, J. B. Nonlactose fermenting organism from the feces of influenza patients. Jour. Infec. Dis., 1920, xxvi, 16.

SMALL, S. C., AND DICKSON, G. K. I. Grouping of bacillus influenzæ by specific agglutination. Jour. Infec. Dis., 1920, xxvi, 230.

SMALL, S. C., AND STANGL, F. H. Influenza at the Cook County Hospital. Jour. Amer. Med. Assoc., 1920, lxxiv, 1004.

SMITH, A. D. Influenza and bronchopneumonia in children. Arch. Ped., 1919, xxxvi, 214.

SMITH, F. M. Tachycardia following influenzal pneumonia. Jour. Amer. Med. Assoc., 1919, lxxiii, 1685.

Somerset, W. L. Epidemic catarrhal fever. Arch. Diag., 1918, xi, 110.

Spooner, Wyman, and Sellards. Serum treatment of Type I pneumonia occurring in association with an epidemic of influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1310.

Stallybrass, C. O. The periodicity of influenza. The Lancet, 1920, i, 372.

Stangl, F. H. Stimulation of meningitis by influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 1048.

Stine, D. G. Chronic influenza. Arch. Diag., 1919-20, xii, 43.

Stivelman, B. Effects of influenza on pulmonary tuberculosis. Arch. Diag., 1919-1920, xii, 118.

Stoll, H. F. Value of convalescent blood and serum in treatment on influenza-pneumonia. Jour. Amer. Med. Assoc., 1919, lxxiii, 478.

Stone, W. J., and Swift, G. W. Influenza and influenzal pneumonia at Fort Riley, Kansas. Jour. Amer. Med. Assoc., 1919, lxxii, 487.

Strouse and Block. Notes of present epidemic of respiratory disease. Jour. Amer. Med. Assoc., 1918, lxxi, 1568.

Symmers, D. Pathologic similarity between pneumonia of bubonic plague and of pandemic influenza. Jour. Amer. Med. Assoc., 1918, lxxi, 1482.

Symmers, Dinnerstien and Frost. Differences in pathology of pandemic and recurrent forms of so-called influenza. Jour. Amer. Med. Assoc., 1920, lxxiv, 646.

Thomson, W. W. D., and Macauley, H. F. Influenza as an etiological factor in nephritis, with an account of four cases of postinfluenzal nephritis. Lancet, 1920, i, 481.

Titus and Jamison. Pregnancy complicated by influenza epidemic. Arch. Diag., 1919-1920, xii, 42.

——— Pregnancy complicated by influenza epidemic. Jour. Amer. Med. Assoc., 1919, lxxii, 1665.

Torrey and Crosh. Acute pulmonary emphysema observed during the epidemic of influenza-pneumonia at Camp Hancock, Ga. Amer. Jour. Med. Sci., 1919, clvii, 170.

Torrey, R. G. Influenzal meningitis, with a report of a case. Amer. Jour. Med. Sci., 1916, clii, 394.

Treupel, G. Ueber chronische Grippe. Deut. Mediz. Wchnschr., 1920, xlvi, 1159.

Tunnicliff, R. Phagocytic experiments in influenza. Arch. Diag., 1918, xi, 169.

——— Phagocytic experiments. Jour. Amer. Med. Assoc., 1918, lxxi, 1733.

——— Observations on the bacteriology of influenza and bronchopneumonia. Jour. Infec. Dis., 1919, xxv, 6.

Underhill, F. P., and Ringer, M. Blood concentration changes in influenza. Jour. Amer. Med. Assoc., 1920, lxxv, 1531.

Utheim, K. Agglutination in influenza. Jour. Infec. Dis., 1920, xxvii, 452.

Vaughan, V. C. Influenza and pneumonia at Camp Grant. Jour. Lab. and Clin. Med., 1918-19, iv, 307.

——— Notes on influenza. Jour. Lab. and Clin. Med., 1918-19, iv, 309.

——— Bacteriology of influenza. Jour. Lab. and Clin. Med., 1918-19, iv, 83.

Vaughan, W. T. Influenza. Jour. Lab. and Clin. Med., 1919-20, v, 403.

——— Significant phenomena of influenza pandemics. Jour. Lab. and Clin. Med., 1919-20, v, 754.

Voille, H. Influenza pandemic. La Presse méd., 1918, xxvi, 1920.

Wade and Manalang. Fungous developmental growth forms of bacillus. Jour. Exper. Med., 1920, xxxi, 95.

Wadsworth, A. B. Bacteriologic investigation of an outbreak of influenza at an institution the inmates of which were previously free from the influenza bacillus when completely vaccinated with influenza vaccine. Jour. Amer. Med. Assoc., 1919, lxxiii, 1657.

Wahl, White and Lyall. Some experiments on the transmission of influenza. Jour. Infec. Dis., 1919, xxv, 419.

Walker, O. J. Pathology of influenza-pneumonia. Jour. Lab. and Clin. Med., 1919-20, v, 154.

Warfield and Ravold. Influenza epidemic at Jefferson Barracks, Missouri. Arch. Diag., 1919-20, xii, 44.

Welk, C. W., and Blankinship, R. C. Intravenous injections of hypertonic glucose solution in influenza-pneumonia. Jour. Amer. Med. Assoc., 1920, lxxiv, 75.

Wells, C. W. Intravenous injections of foreign protein in influenza-pneumonia. Jour. Amer. Med. Assoc., lxxvii, 1818.

Winchell and Stillman. Occurrences of bacillus influenzæ in the normal throat. Jour. Exper. Med., 1919, xxx, 497.

Winslow and Rogers. Influenza in Connecticut, with a consideration of the factors which influenced the prevalence of this disease in various communities. Jour. Infec. Dis., 1920, xxvi, 185.

Winternitz, M. C. The pathology of influenza. Yale University Press, 1920.

Wolbach, B. Comments on the pathology and bacteriology of fatal cases as observed at Camp Devens, Mass. Bull. Johns Hopkins Hosp., 1919, xxx, 104.

Woolley, P. G. Transmission of influenza. Jour. Lab. and Clin. Med., 1918-19, iv, 372.

——— The epidemic at Camp Devens. Jour. Lab. and Clin. Med., 1918-19, iv, 330.

——— Toxin of bacillus influenzæ. Jour. Lab. and Clin. Med., 1918-19, iv, 377.

Woolstein, M. Pfeiffer's bacillus. Serological study. Jour. Exper. Med., 1919, xxx, 555.

Woolstein and Spence. Bacillus of Pfeiffer in inflammations of the respiratory tract in children. Amer. Jour. Dis. Child., 1920, xix, 459.

Woolston, W. J., and Conley, D. O. Spanish influenza in pregnancy. Jour. Amer. Med. Assoc., lxii, 1898.

Wynn, W. H. Protective inoculation against influenza. Brit. Med. Jour., 1920, i, 254.

Yabe, S. Leukocytes in influenza. Arch. Exper. Med., 1921, iv, 109.

CHAPTER L

ACUTE POLIOMYELITIS

By Harold L. Amoss, M. D.

Definition, p. 335:
Etiology, p. 336—The virus, p. 337; Cultivation experiments, p. 338.
Pathology, p. 339—Microscopic, p. 340; Distribution of microscopic lesions in the brain and cord, p. 342; Lesions outside the central nervous system, p. 343.
Symptomatology, p. 343—Pain, p. 345; Sphincters, p. 345; rashes, p. 345; Blood, p. 345; Spinal fluid, p. 346; Reflexes, p. 347; Paralyses, p. 347.
Diagnosis, p. 348—Examination, p. 348; Lumbar puncture, p. 349; Differential diagnosis, p. 349.
Treatment, p. 350—Serum treatment, p. 350—The serum, p. 350; Collection of serum from donor, p. 350; Amount injected, p. 351; Results, p. 351; General treatment, p. 352; Drugs, p. 352; Treatment of paralyses, p. 352; Prevention, p. 352; Distribution of virus in the host, p. 353; Routes of infection, p. 354; Mechanisms of defense, p. 355; Carriers, p. 356; Communicability, p. 357; Isolation, p. 357; Individual prophylaxis, p. 357; Instruction during epidemic periods, p. 358.
Prognosis, p. 358.
Historical, p. 358.

Definition.—Acute poliomyelitis is an infectious, contagious, communicable disease resulting from the growth of a filter-passing virus in the central nervous tissues with symptoms first of a systemic infection and then, in some cases, of those referable to lesions of the cord and brain. The disease may appear in isolated (sporadic) instances, or in epidemic proportions.

The large epidemics of the past thirty years have stimulated research in various countries with the result that the sum total of our knowledge of poliomyelitis is considerable.

The attention formerly bestowed on the paralysis as the outstanding feature is now turned to the infectious nature of the disease. Caverly's[1] observations in the Vermont epidemic of 1894 called attention to a small group of cases having the symptoms of acute poliomyelitis but without demonstrable paralysis. In Wickman's[2] wider experience this group was more definite and the cases were described by him as "abortive." It seems best to refer to them as the non-paralytic group, reserving the former term for the truly abortive cases.

As experience in the recognition of acute poliomyelitis increases, especially with the aid of examination of the spinal fluid, the percentage of non-paralytic cases is raised. Since the percentage is changing from time to time, and varies in different epidemics, an exact figure representing this relation cannot be given. One is safe at present in making the statement that from 40 to 60 per cent. of all epidemic cases do not become paralyzed. This is one of the most important points in the study of the disease, from either clinical or public health aspects.

The prominent general symptoms revealing the onset, especially in epidemic periods, have been accepted by most modern clinicians as evidence that poliomyelitis is first a generalized infection which may or may not localize in the central nervous system. Draper[3] has described a group of cases in which there was a gastro-intestinal disturbance, followed by an asymptomatic period of from three to seven days preceding the actual onset of the poliomyelitic attack. He regards the primary attack as response to the invasion of the virus. The author has encountered such cases in Westchester County, New York, and in Vermont. If Draper's interpretation is correct, these observations lend support to the hypothesis of a preliminary generalized infection.

However, the author is not yet ready to accept this view, though he agrees that the clinical picture at the beginning of the acute infection strongly suggests a general infection.

On the other hand it appears that such symptoms may arise from a localized infection of the meninges, as in tuberculous meningitis. Moreover, in poliomyelitis stiffness of the neck reflecting meningeal irritation appears almost coincident with the general symptoms, suggesting a localized infection. The earliest symptoms of experimental poliomyelitis in the monkey also suggest a generalized infection, though in less degree; yet when huge doses of the virus are injected intravenously in this animal, no signs appear unless the virus localizes in the central nervous system after an incubation period of from seven to twelve days, during which time the animal seems perfectly well.

There is no indication from experimental studies that the virus multiplies in any tissues except the central nervous system, or provokes symptoms by its presence in the other tissues. It seems, therefore, that the general symptoms can be explained on the basis of localization of the virus in the meninges.

Etiology.—Even in the larger epidemics where it may be presumed that the virus is widely distributed, the susceptibility rate is remarkably low. For example, in the epidemic of 1916 there were 9,005 cases in New York City[4] where the attack rate per 1,000 of total population was 3.8. The rate among persons over 10 was very much lower, *i. e.*, 0.23. The attack rate in various age groups is given in the following table.[4]

TABLE I

ATTACK RATE PER 1,000 POPULATION AND AGE DISTRIBUTION IN 1916 EPIDEMIC IN NEW YORK CITY

Age Group	Rate per 1,000 Population	Percentage of all Cases*
Under 1 year	18.4	3.5
1-2 years	34.24	14.6
2-3 years	41.01	25.5
3-4 years	29.85	20.1
4-5 "	18.04	12.7
5-6 "	13.23	7.6
6-7 "	7.73	4.5
7-8 "	5.15	3.0
8-9 "	3.72	2.3
9-10 "	2.70	1.5
10 years and over	0.23	4.7

*Based on a study of 5,432 out of 9,005 cases.

In the last column of Table 1 is given the age distribution based on a careful study of over half the cases in New York City. The figures correspond closely with the distribution in the Swedish and Vermont epidemics with one exception: whereas in the New York epidemic 97 per cent. of the cases were among children under 16 years and 3 per cent. among persons older; in Vermont the figures are 90 per cent. and 10 per cent. respectively. We have at present no explanation for the higher adult rate among the rural population (Vermont). There are two other points of distinction in the epidemiology of poliomyelitis in New York City and Vermont. In all areas the outbreaks are essentially summer epidemics, but the peak in Vermont coming usually the first or second week in September, is about two weeks later than in New York. It is probable that the season plays an important rôle here. The other difference lies in the yearly distribution of cases. In New York there are relatively few cases in the interepidemic years, but Vermont is visited each year by small outbreaks, with a large wave recurring every four or five years. The distribution in Massachusetts is much the same as in Vermont though the epidemic rate is not so high. The difference in density of population cannot be the sole determining factor, since Massachusetts is essentially urban.

Because of the low attack it was formerly believed that only one case occurred in any family. In the New York epidemic 2 cases occurred in 290 families; there were seventeen instances of 3, two of 4, and two of 5 cases in one family. The author in the same epidemic in Westchester County, N. Y., observed 4 cases in a family of five children.

The Virus.—The infectious nature of poliomyelitis became evident from the clinical and epidemiological observations of Wickmann, but definite proof came from animal experimentation. In 1909 Landsteiner and Popper[5] produced experimental poliomyelitis in a monkey by injecting intraperitoneally a suspension of the central nervous tissues of a human case. Straus and Huntoon[6] were also successful in a similar experiment. A few months later Flexner and Lewis[7] reported their success in transferring the disease from monkey to monkey where others had failed. Flexner and Lewis injected the suspension of poliomyelitic tissues directly into the brain. With this method the virus was established in monkeys and the same strain has now been passed through several hundred monkeys. For the first few transfers in monkeys relatively large amounts of suspensions of poliomyelitic nervous tissues are required to reproduce experimental poliomyelitis, but after three or four passages the virus becomes established in that species, so that 0.001 c.c. (.016 minim) or less of a 5 per cent. suspension representing 1/500,000 gram of nerve tissue suffices. Thus the introduction of this minute amount into the brain of a monkey of which the central nervous system weighs 90 grams results in the activation of the total mass which in turn becomes capable of infecting other monkeys even in minute doses. There is no conclusion possible other than that the etiological factor is a living organism and multiples in the tissues. But microscopic examinations of the poliomyelitic tissues reveal no visible microörganisms. Therefore, the microörganisms must be either beyond the range of the microscope or of such a character that they do not take the stain. It soon became known that the virus would pass through the Berkefeld filters. The water-clear filtrate capable of producing experimental poliomyelitis contains no bodies visible with the dark-field microscope. The microörganism of poliomyelitis is therefore classified as a filter-passing ultramicroscopic virus.

The virus is very susceptible to drying, to sunlight, hydrogen peroxid, chlorin, and mercuric chlorid, but peculiarly resistant to phenol. A Berkefeld filtrate containing 0.5 per cent. phenol or in contact with ether has been found active in the author's laboratory after standing five days at room temperature. The thermal death point is about 50° C. (120° F.). Methods for disinfection are obvious from the above data.

Cultivation Experiments.—The most convincing results are reported by Flexner and Noguchi.[8] In ascitic fluid containing fresh rabbit kidney these authors succeeded, after many trials, in growing a minute anaërobic globoid from poliomyelitic tissues (Fig. 1). Pure cultures, when injected intracerebrally, intraspinally, or intraperitoneally into the monkey reproduced typical experimental poliomyelitis, and from the central nervous system of the monkeys injected the globoid bodies were again isolated. After transfer in the kidney-ascitic fluid, the bodies lose their parasitic nature after the eighth or tenth passage and become more saprophytic. A critical experiment with a culture of globoid bodies was carried out by Flexner, Noguchi and Amoss.[9] Mass cultures from the eighth transfer which had remained in the same tube at 37° C. (98.6° F.) after thirteen months were injected intraspinally into one monkey and intraperitoneally into another at weekly intervals for three weeks, and the monkeys thus far remained apparently normal. However, after a fourth injection both monkeys came down with typical experimental poliomyelitis, and from these monkeys and succeeding monkey passages the globoid bodies were recovered. Control experiments showed that the virus under the conditions of cultivation may live for twenty-one days but not for thirty days at 37° C. if no growth appears. In this experiment the original virus has been diluted at least 80,000 times and had remained for over five hundred days in the incubator. Amoss and

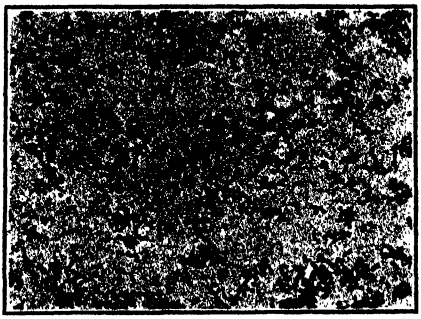

Fig. 1.—Globoid Bodies. X 1,000.

Smillie[10] and Gates have repeated the cultivation experiments of Flexner and Noguchi, and Amoss[11] has found, in incubated poliomyelitic brain, small bodies morphologically and tinctorially identical with the Flexner-Noguchi organism. Thus Koch's postulates have been fulfilled, but Amoss[12] has failed to discover any immunological relation between the globoid bodies and the filterable virus. It is possible that the globoid bodies constitute another form of the virus. There is no evidence that the virus in tissues exists in the form of the visible globoid bodies.

Rosenow, Nuzum, Matthews[13] and others have isolated from poliomyelitic tissue pleomorphic streptococci which in one stage resemble globoid bodies and pass through a Berkefeld filter, but Bull[14] has shown that none of the streptococci is capable of producing experimental poliomyelitis. They are obviously secondary invaders, since they may be recovered from central nervous tissues of persons who have succumbed to other diseases.

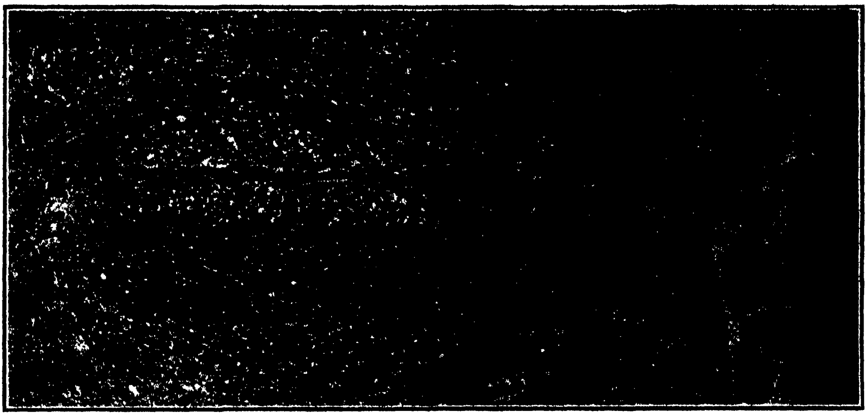

FIG. 2.—MENINGEAL REACTION, SPINAL CORD.

The following experiment shows clearly the relation of streptococci to poliomyelitis: A monkey is etherized on the first day of prostration of experimental poliomyelitis; the brain and cord contain the virus, but streptococci are usually absent. Another monkey is allowed to die from experimental poliomyelitis; streptococci almost always are present in the central nervous system. The human case corresponds to the second monkey.

Pathology.—The gross appearances in the uncut brain and cord of the human case and the experimental disease may not present any abnormality except a slight bulging of the mass, when the dura is cut. In many cases the meninges are congested. On section the brain and cord are moist and seem to be slightly swollen. There is usually congestion of the capillaries of the grey matter, sometimes of the white substance, and here and there petechial hemorrhages. A cross-section of the cord, especially through the cervical and lumbar enlargements, brings out the chief macroscopic change. At one or both of these levels the grey matter rises slightly above the cut surface and varies from a diffuse pink with occasional capillary hemorrhage to an obvious hemorrhagic myelitis. The lesion may be present in the lumbar enlargement and diminish in intensity in succeeding proximal sections; also the lesion may be present in the cervical and diminish in succeeding distal section.

In human cases the medulla is usually distinctly congested, although it often happens that no lesion is visible macroscopically.

MICROSCOPIC.—The virus provokes a round cell reaction. There is always more or less response in the meninges, especially around the blood-vessels in the pia (Fig. 2). The reaction may be mild and localized at certain levels of the cord, or intense (Fig. 3) and generally distributed.

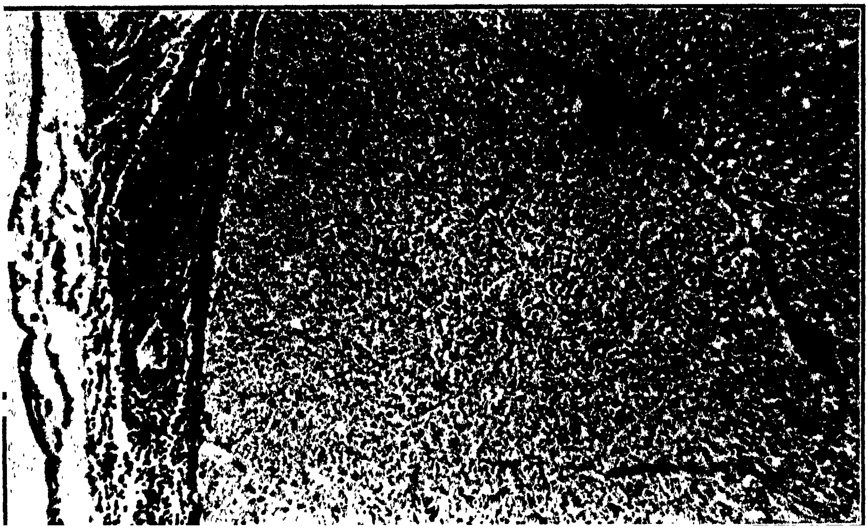

FIG. 3.—PERIVASCULAR INFILTRATION IN THE WHITE MATTER AND INTENSE MENINGEAL REACTION.

A few polymorphonuclears and cells of local origin may be found among the lymphocytes. The meningeal reaction is probably the first lesion in the disease and is the logical basis of the clinical neck and back sign.

The next lesion in order of occurrence lies in the posterior root ganglia. Here the usual picture is that of focal infiltration of small lymphocytes accompanied by a midinterstitial hyperplasia and various degrees of nerve-cell destruction (Fig. 4). The latter progresses in the same manner as in the motor cells in the cord to be described later. The posterior root ganglia are the first nerve tissues to be attacked and are also the first to recover. It is remarkable that with such extensive lesions as sometimes occur, there are no residual disturbances of sensation. The changes in the posterior root ganglia probably explain the exquisite hyperesthesia. The lesions in the Gasserian, ophthalmic, and sympathetic ganglia correspond to those described in posterior root ganglia.

In the substance of the cord both the white (Fig. 3) and the grey matter are affected. The lesion in the former consists of perivascular infiltration (Fig. 5) about the capillaries, slight edema, and sometimes hemorrhage. It is the grey matter which suffers most. Much attention has been directed to the changes in the anterior horns, however, the posterior horns are nearly as often involved in the acute process.

There are focal, perivascular, and diffuse infiltrations of round cells (Fig. 6) and edema, especially around the blood-vessels and the nerve-cells. The blood-vessels in many instances are still further damaged, resulting in small or extensive hemorrhages. The blood-vessels outside the central nervous system are apparently not damaged to this extent.

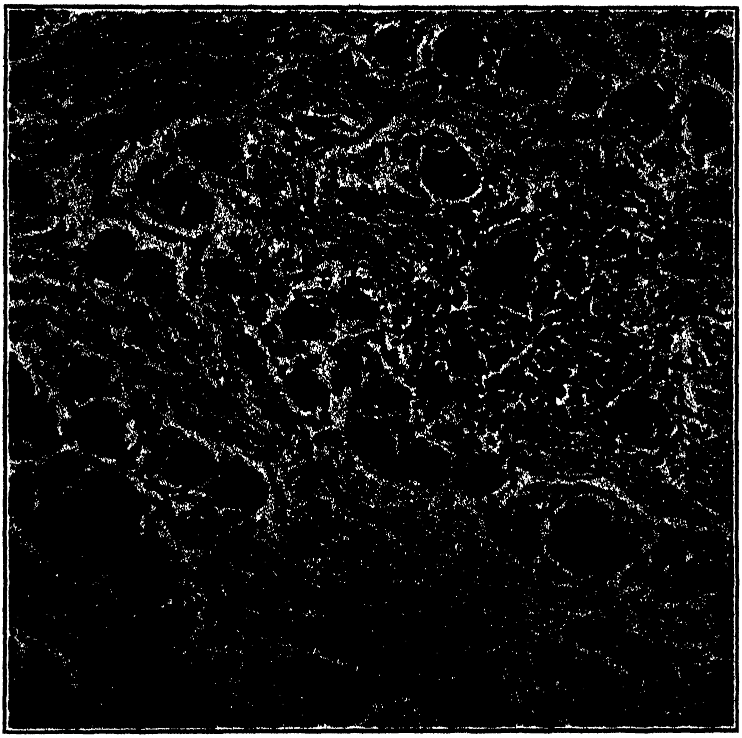

FIG. 4.—FOCAL INFILTRATION AND NEUROPHAGOCYTOSIS IN THE POSTERIOR ROOT GANGLION.

It would seem, therefore, that the injurious effect is associated with the multiplication of the virus. The nerve-cells seem to be especially susceptible either to the direct or indirect effects of the virus. Examples of the changes to be described may be seen in a single section (Fig. 7). The sequence of the cell changes has been followed by killing monkeys at various stages in experimental poliomyelitis, of which the first step is the perineurotic edema. Later the protoplasm of the cell becomes granular, the nucleus loses its finer markings and stains more faintly. During this time neurophages are arranging themselves about the cell, and the protoplasm of the periphery seems to dissolve leaving a coarse, granular débris, and coincidently the neurophages insinuate themselves into the dead cell. After solution is complete, scar tissue fills the space previously occupied by the nerve-cell.

Permanent damage to the nerve-cells results in paralysis and if, by chance, the respiratory centers are involved, death ensues. It is a point of especial importance that cells damaged to the extent that they do not function, may recover, as shown by the occasional rapid recovery of completely paralyzed muscles. This fact suggests the edema as the immediate cause of the inability of the cell to function. The pressure and isolation of the cell from fluid and gaseous interchange would be expected to affect the function of the cell and, if prolonged, lead to its death. Some attempts have been made, by intravenous injection of hypertonic solutions, to ascertain whether the nerve-cell injury is due to edema or to a toxin. But edema is apparently not a question of osmotic pressure alone. There is no positive evidence of the presence of toxins, and since toxins are usually firmly bound and recovery of nerve tissues is slow after toxin union, it is difficult to reconcile the rapid restoration of function with the hypothesis that the damage resulted from this cause. The question must be left open with the weight of evidence towards the edema factor.

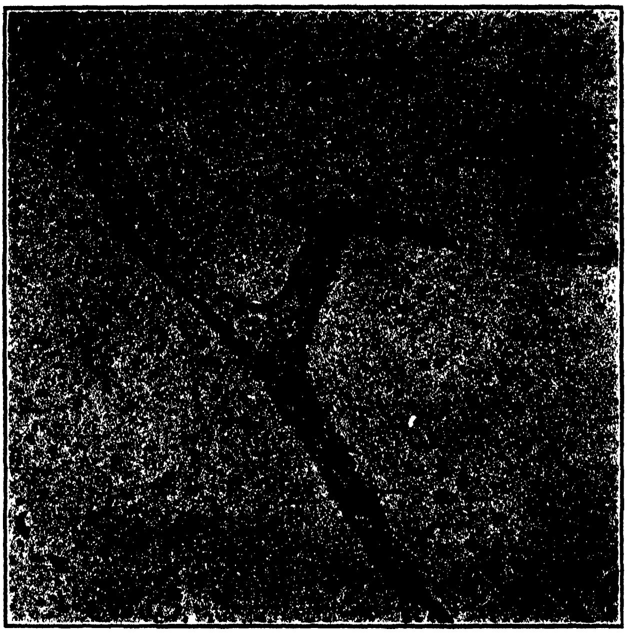

FIG. 5.—PERIVASCULAR INFILTRATION IN THE SPINAL CORD.

DISTRIBUTION OF MICROSCOPIC LESIONS IN THE BRAIN AND CORD.—In the majority of human cases the lesions are present in the medulla though they may be slight. The cord is more often involved than the brain, but in both the distribution is irregular. In the cord the lesions are more often present in the cervical and lumbar enlargements, while in the brain a frequent site is beneath the floor of the fourth ventricle. The basal ganglia and subcortical regions of the cerebrum are sometimes involved, and lesions may also be present in the cerebellum.

At autopsy it is the custom to take blocks from the cortex, basal ganglia, medulla just above the calamus, cervical and lumbar enlargement, middorsal and at least two posterior root ganglia from the cervical and from the lumbar level.

Lesions Outside the Central Nervous System.—All the lymph glands, including the lymphatic tissue of the spleen are hyperplastic.[15] The virus is found in these tissues. In the liver small focal infiltrations of round cells are found sometimes with small areas of necrosis. The hepatic changes in human cases vary and are sometimes found only after diligent search.

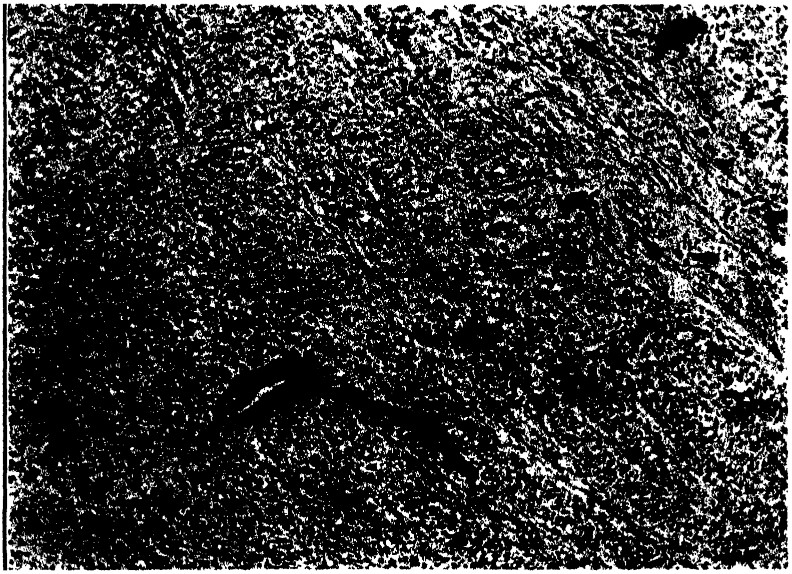

Fig. 6.—Perivascular and Diffuse Infiltration in the Medulla.

Symptomatology.—With few exceptions, acute poliomyelitis begins more or less suddenly with general symptoms. A previously healthy child seems out of sorts and listless, with loss of appetite. During epidemic periods in from 25 to 40 per cent. of all cases, a history of an upset from three to ten days previously may be elicited. Draper has described a series of such cases and believes that the first attack represents the invasion of the virus. Usually the indisposition passes quickly and the child remains well until the second phase or definite attack of acute poliomyelitis is evident. This is the so-called "dromedary" type. In 9 cases out of 10, there are gastro-intestinal disturbances, either diarrhea or constipation. When diarrhea is present, it is of short duration and later in the attack constipation is the rule. The patient usually vomits only a few times and the mother is prone to ascribe the upset to dietary indiscretion, such as too much fruit, pastry, cheese, or canned goods, as the vomiting is not projectile or different from the type usually associated with gastro-intestinal upset. A dull headache is the rule; however, the author has seen a few cases in children old enough to describe their sensations in which this symptom was absent. Most of the patients are drowsy, but can be aroused. Some are restless and excited, and rarely there is delirium. Fever is almost always present. The temperature is usually from 100° to 102.5° F. (37.8° to 39.2° C.) though it may reach 105° F. (40.6° C.), endures for a variable period from a few hours to three or four days, and rapidly returns to normal. The febrile period may come and pass unobserved during the night and the only history obtainable may be that of a wakeful, fretful

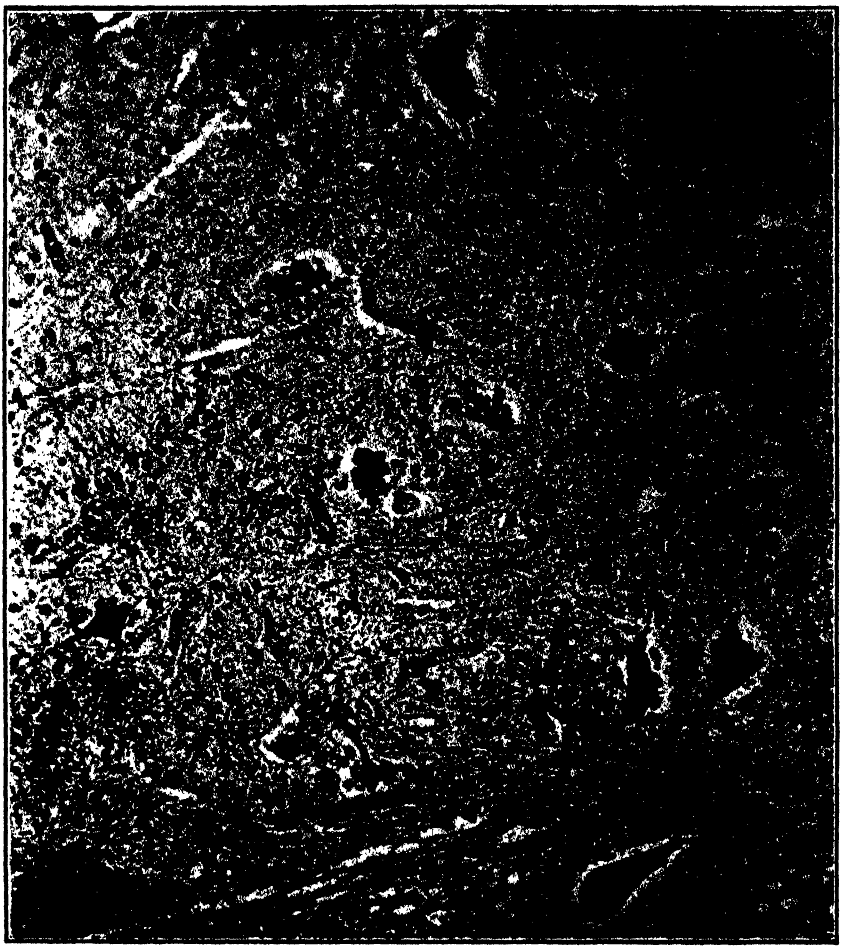

FIG. 7.—NEUROPHAGOCYTOSIS, HEMORRHAGE, AND EDEMA IN THE SPINAL CORD.

period during which the child called for water. It is this type of case in which the child, having passed through the unrecognized brief acute attack, is improved and a day or two later gets up in the morning with a group paralysis (so-called morning paralysis). At the onset the patient is flushed and presents a picture of the onset of the acute diseases of childhood, yet there is a difference often obvious to the experienced mother, for the sclera are slightly dulled and the face seems glazed over. It is as though the patient were being seen through smoked glasses. The pulse rate is usually accelerated to a greater extent than can be accounted for by the fever.

PAIN.—Besides the headache, which in certain cases may be severe, the patient often complains of pain in the neck or between the shoulders and in the back. The pain is accentuated by the stretching of the neck when the patient's head rests on pillows. Pains in the legs, hips, or arms may appear suddenly in the night, sufficiently severe to awaken the sleeping patient. Groups of muscles may be very sensitive to pressure or passive movement. One of the most distressing symptoms is the exquisite hyperesthesia of the skin in less than half the cases. It usually lasts from five to ten days and is prolonged by pressure of the bed clothing or massage. The author knows of one case in which the hyperesthesia lasted thirty days. The rare occurrence of hypesthesia and anesthesia in poliomyelitis has been noted by foreign observers, but the author has not prolonged the neurological examinations to this extent in his acute cases.

General profuse or local areas of sweating on the head or back of neck, or on an arm or leg, appear in some cases. Flushing of the skin or, more often, blanching of an arm or a leg is often the precursor of paralysis in that member.

SPHINCTERS.—Retention of urine and stools is common, necessitating catheterization and enemata. Marie[21] reports the rare occurrence of retention.

RASHES.—Morbilliform or scarlatiniform rashes with heavily coated tongue, congested throat, and occasional minute red spots in the buccal mucosa, have been noted by some observers[22] in otherwise uncomplicated cases of acute poliomyelitis, but in over 1,100 cases the author has not encountered these signs. Herpes is exceptional.[21]

BLOOD.—It is generally accepted that abnormal white blood counts are constantly found in poliomyelitis, but opinion is divided on the characteristics of this change.

Müller[16] asserts that a distinct leukopenia with a relative lymphocytosis is characteristic and pathognomonic of the febrile stage, while La Fetra[17] had previously described a moderate leukocytosis as being characteristic of the acute stage in human beings.

Gay and Lucas[18] summarize their blood findings as follows: "The acute stage of anterior poliomyelitis as it occurs in human beings, and as it is produced experimentally in monkeys, is characterized by the occurrence of a distinct leukopenia. The differential count shows a relative increase in number of eosinophils and lymphocytes."

Peabody, Draper and Dochez[19] found in human cases a constant and marked leukocytosis. They also found a constant increase in polymorphonuclear cells of from 10 to 15 per cent. and a diminution of lymphocytes of from 15 to 20 per cent.

H. D. Taylor[20] made blood counts on 6 series of monkeys before and at various intervals after inoculation with poliomyelitic virus, and used as a basis of comparison averages of 121 counts on 40 normal monkeys. He found that "all the counts made on monkeys during the course of typical acute experimental poliomyelitis show a variation from the normal;" and "after injection of active poliomyelitic virus the lymphocytes are diminished but return to their former number and are actually increased between the fourth and sixth days of the incubation period. The polymorphonuclear count is high at this time. The normal average of lymphocytes of 11,815 is increased to an average of 19,696 though the average percentage is slightly lowered. During the first 3 days after onset a marked diminution in the lymphocytes takes place. Thus, instead of an average normal lymphocytic count of 11,815 the number is 3,302, and the average percentage is 15.6. At this time the polymorphonuclear neutrophilic leukocytes are materially increased in number (18,231) as compared with an average normal of 9,116, and the percentage is also increased from an average of 41 to 84 per cent. of the total white cells. When the monkeys become completely prostrate, metabolism is at low ebb, and there occurs a further decrease in the actual number of lymphoctyes which remains low for long periods. The total number of polymorphonuclear neutrophilic leukocytes returns to normal, but there remains a relative increase averaging 77 per cent. Finally, during recovery both types of cells return to the average normal count and relation. No stimulation of the lymphocytes above normal appears during recovery."

SPINAL FLUID.—Invaluable information is to be gained by microscopic and chemical examination of the spinal fluid, since from the beginning of the acute attack abnormal findings are the rule. The fluid is usually clear and under slightly increased pressure and occasionally is slightly turbid. During the first day the cell count is above normal and increased: the average count is from 40 to 100 cells per cubic millimeter, and counts from 400 to 500 are fairly common. Fewer cases have counts of from 500 to 1,000. The author has observed one case in which the number was 1,200, and Draper reports the high limit of 2,500. A count above 10 per cubic millimeter is to be regarded as normal.

The earliest cells to make their appearance in the spinal fluid are multilobed and blob or smudge cells probably of local origin, but soon small round cells outnumber the others. It is highly important to note the type of cells present. Interpretation of the findings will be discussed under diagnosis.

A slight excess of globulin appears usually on the second day and gradually increases each day for several days. Excess of globulin persists after the cells have disappeared. The colloidal gold reaction of Lange shows a weak luetic zone curve. No specific complement-fixation test has been discovered in the spinal fluid in poliomyelitis.

Reflexes.—In the large majority of cases the reflexes are disturbed at one time or another, but there is no rule. In general, the reflexes tend to be asymmetrical, and there seems to be a greater tendency to variation of the reflexes of the lower half of the body. The variations from normal are more likely to be towards diminution or abolition than to a hyperactive state. Hyperactivity, when present, is usually very early in the course of the acute attack, later disappearing and the response being lost altogether. Disturbances of reflexes in a muscle group can be interpreted usually as foreboding paralysis; however, reflexes may be absent to return without subsequent paralysis in that group. Extensor response after plantar stimulation (Babinski) is sometimes present, indicating a pyramidal tract lesion.

Paralyses.—Twitching of muscle groups often occurs during rest or sleep in the early periods of the attack. These signs and intention tremors usually forebode paralyses in those muscles. Formerly the paralyses attracted undivided attention, and diagnosis of acute poliomyelitis was not made until the palsies were definite. It is now common knowledge that paralyses are not essential to the diagnosis and that they may be regarded as occurrences or complications in the course of an infectious disease. While a few cases of spastic paralysis have been described in poliomyelitis, flaccidity may be regarded as characteristic of this disease. Of particular importance in diagnosis and prognosis is the partial or complete recovery of a paralyzed muscle sometimes within a few days.

Over 60 per cent. of the paralyses appear within the first 3 days after onset. The following table based on 200 cases reported by Lovett and Sheppard[23] shows the time of appearance after onset:

Same day	10	per cent. of all cases.
One day	15	" " "
Two days	20	" " "
Three days	17	" " "
Four to seven days	26	" " "
Eight to twelve days	7	" " "
Over twelve days	5	" " "

The parts in which paralysis appeared early in 759 cases is shown in the following table:

Distribution of Early Paralysis

One leg only	145	cases
Both legs only	146	"
One arm only	44	"
Both arms only	12	"
One arm and leg, same side	50	"
One arm and leg, opposite sides	18	"
Both legs and one arm	32	"
Both arms and one leg	8	"
Both arms and both legs	51	"
Ataxia (transitory)	7	"
Abdomen	38	"
Back	79	"
Neck	13	"
Respiration	89	"
Deglutition	12	"
Intercostal	1	"
Face	7	"
Right face	31	"
Left face	24	"
Strabismus	2	"
	759	"

There has been considerable discussion on the classification of clinical types. Since the lesions may be widely distributed in the central nervous system, there is great possibility of overlapping. There are some cases, however, in which it is evident that the lesion is more marked in definite areas. For example, in some the meninges seem to bear the brunt of attack. In these cases the cells in the spinal fluid are greatly increased and the symptoms referable to an inflammatory reaction suggests a pyogenic meningitis. Another form deserving special mention, the most alarming type to the inexperienced physician and to the family, is that in which the patient passes quickly from an excited stage with clouded intellect and sometimes delirium into stupor. Paralysis may appear, but fortunately the prognosis is more favorable than the condition seems to warrant. This form has been described as the encephalitic type. The most distressing form is characterized by paralyses referable to the medulla, particularly when the respiratory center is being encroached upon. There is hope, however, in the fact that even in complete intercostal or diaphragmatic paralysis, the temperature may sometimes drop to normal, and soon afterwards the respirations improve and the patient recovers, but any involvement of the respiratory center augurs a grave prognosis.

It is nearly always true that the initial is the final paralysis, and once begun, the final stage of paralysis is soon reached. In a relatively small number of cases, there is a successive involvement, first of the lower extremities, then of higher groups, until the respiratory center is involved and death results (ascending, or Landry's type). The descending type is less frequently seen, and the outlook is more favorable. In the Landry type, the ascent of the paralysis may be arrested, but until the temperature is normal the danger is not over. The author saw one case in which both legs were completely paralyzed, and for three days there was no further involvement but the fever remained and suddenly the bladder, abdominal, and intercostal muscles in turn failed. Serum was given in large doses at this point and the patient recovered the use of all muscles involved in the second stage, but not of those involved in the first period.

Diagnosis.—In epidemic periods, diagnosis of poliomyelitis can be made before the onset of paralysis. A child with a gastro-intestinal upset, headache and fever, less alert and bright than with ordinary fevers, somewhat cranky and unapproachable should be examined more carefully with the possibility of poliomyelitis in mind.

EXAMINATION.—Such a child is difficult to examine. The friendly and tractable child becomes suspicious and distrustful and is obviously annoyed by the approach of the physician. It is even more difficult for the consultant, as the patient has learned from the previous examinations that stretching of the neck and back and passive movements are painful. This is especially true when there is already an involvement of the posterior root ganglia. A few minutes devoted to making friends with the patient is very helpful, as much depends upon coöperation. Before any manipulation, the chest and abdomen should be observed carefully to note any intercostal or diaphragmatic paralysis. To test the intercostals, the diaphragm is immobilized by pressure with both hands on the abdomen, and likewise the intercostals are immobolized by pressure on the chest to test the function of the diaphragm. The examination should be made gently and quickly. It is inadvisable to subject the patient to a prolonged and exhausting neurological examination at this stage. After the usual physical examination, leaving the pharynx to be examined last, the reflexes are tested quickly with a soft rubber hammer (Thomas type).[24] In addition to the abdominal and plantar response, valuable information is often obtained by stroking the plantar surface and simultaneously palpating the inner hamstring on the same side. In carrying out the hamstring test, the patient's knee is slightly flexed. The normal response is a tightening of the hamstring, but in poliomyelitis there is often a response on one side but not on the other.

If there is no involvement of the respiratory center and there are no other contra-indications, the patient is allowed to sit on the side of the bed. In early poliomyelitis, the patient assumes a characteristic attitude: The back is held straight and both hands rest on the bed slightly behind the buttocks with arms straight and stiff in an attempt to take the strain from the painful back. When the patient is asked to bend over and place the head between the knees, the back is held straight and the patient bends only from the hips. This is one of the most constant of all signs in acute poliomyelitis. Additional evidence of the tender spine is obtained in manipulation for Kernig's sign, the response to which is not a true reflex. Finally the attempt is made to bring the chin to the chest by anterior flexion of the neck and in nearly every case the neck is resistant and the manipulation causes pain. Here again there is not true rigidity but voluntary effort for protection. The author has seen only a very few cases in which in the early stage the neck was not stiff, and as the neck and back signs may be regarded as a constant symptom, their presence in a child with an acute onset without discoverable cause suggests inflammation of the meninges. Even in the absence of other signs pointing to poliomyelitis or meningitis, spinal fluid should be withdrawn.

LUMBAR PUNCTURE.—Before withdrawing fluid, it is important to have a microscope with a counting chamber and reagents for the gobulin test (butyric acid[25] or phosphate,[26] or Noguchi's colloidal reagent[27]) ready for immediate use. The findings in the spinal fluid form only a part of the clinical data necessary for differential diagnosis, and since the changes are not pathognomonic, they must be viewed for interpretation with the stage of the disease well in mind.

DIFFERENTIAL DIAGNOSIS.—There are three diseases which in the earlier stages are most likely to be confused with acute poliomyelitis. They are epidemic meningitis, tuberculous meningitis, and epidemic encephalitis. Obviously, only a few of the differential points can be given here.

Epidemic meningitis referable to high portions of the cord may in rare instances begin with a group paralysis. In the first few hours, the number of cells in the spinal fluid may be well within the upper limits of the numbers found in acute poliomyelitis and many of them round cells in the proportion not exceptionally found in poliomyelitis, but the globulin tests show a much heavier precipitate than occurs at this state in poliomyelitis. There is a true reflex rigidity of the neck and back instead of the voluntary stiffening in poliomyelitis. The body surfaces should be searched carefully for red splotches.

Tuberculous meningitis often begins with a gastro-intestinal upset similar to that observed in poliomyelitis, and the latter especially in young children may offer the typical text-book picture of tuberculous meningitis with strabismus. Chemical examination of the spinal fluid usually gives the clue, as the cell content in both diseases may be identical, but in tuberculous meningitis the excess of globulin appears early in the course of the disease. In tuberculous meningitis close questioning usually brings out the history of a period of indisposition, failing appetite, and lassitude before the actual onset, whereas in poliomyelitis, this history is lacking.

Epidemic encephalitis, without localizing signs, and the encephalitic form of acute poliomyelitis may simulate one another so closely as to present a difficult problem in differential diagnosis, especially in the early stages. The diffuseness of the lesions, an exaggeration of the stupor and clouded psyche point toward epidemic encephalitis. Also the encephalitic form of poliomyelitis occurs only during epidemics of that disease. The spinal fluid findings assist in about half the cases. In epidemic encephalitis, the fluid is abnormal in about 50 per cent. of all cases and the cell count in these is usually not as high as is generally found in the encephalitic type of poliomyelitis. Doubtless cases will occur in which the diagnosis must be deferred. The course of the encephalitic form of poliomyelitis is relatively short, but mortality is low, and in recovered cases there are no sequelæ which are confused with the distressing aftermath of epidemic encephalitis. In fatal cases of poliomyelitis death occurs (respiratory failure) by the seventh day, while in epidemic encephalitis the end comes later, usually not earlier than the eighth day.

Treatment.—SERUM TREATMENT.—The basis of serum treatment rests upon the observation of Römer and Josephs[29] that immune bodies are present in the blood of recovered cases. The experiments of Flexner and Lewis[30] show that the injection of such serum delays and may prevent altogether the development of paralysis in monkeys previously inoculated with the virus. Netter[31] was the first to treat human cases. Since the lesion is tucked away in the most remote and inaccessible part of the body the treatment becomes a difficult and almost insurmountable task.

The Serum.—In the absence of any immune animal serum, recourse must be had to convalescent serum which is obviously weak in antibody content when compared with hyperimmune serum such as is employed in the treatment of meningitis. **Serum from recently recovered cases** is recommended, as it is presumed to have a greater antibody content. **The serum for intraspinal injection should be free of particles and hemoglobin.**

Collection of Serum from the Donor.—Obviously the donor should be free from infectious disease and the blood Wassermann negative. In epidemics, the author has collected serum from suitable cases six or eight weeks after onset. As much blood as can be safely withdrawn (from 200 to 500 c.c. according to the weight of the patient) is collected in sterile centrifuge tubes or convenient sterile flasks, care being taken to direct the stream so that there is the minimum amount of damage to the red cells. The blood is allowed to clot and stand at room temperature over night. The serum is drawn off, centrifuged, and inactivated at 56° C. (132.8° F.) for one-half hour. After testing for sterility, it is preserved with 0.35 per cent. tricresol, re-centrifuged, and placed in 20 c.c. bottles which are kept in the icebox. Samples of serum from several sources when available are given consecutively in one treatment. In emergency cases, the blood may be withdrawn from the donor into a sterile flask containing sufficient sodium citrate (chemically pure) to prevent coagulation, and immediately centrifuged and the plasma used for intravenous injection only.

Amount Injected.—Since at best only weakly immune serum is available, correspondingly larger amounts of serum must be given. Obviously the amount of serum which can be injected intraspinally is limited, and Draper[8] has called attention to the severe reactions which follow the intraspinal injection of large amounts. On account of this limitation and for other reasons about to be described, the author has used the combined route of intraspinal and intravenous injections.[32] Flexner and Amoss[33] found that poliomyelitis antibodies in the blood would pass into the spinal fluid if the meninges were inflamed, and Amoss and Eberson[34] showed that the disappearance of antibodies from the spinal fluid in meningitis proceeds at a slower rate if immune serum is also injected intravenously.

The author's procedure follows: After withdrawal of the spinal fluid the needle is left inserted and the lumen stopped with the stylet, so that no more fluid escapes. Samples of the fluid are examined microscopically and chemically within seven minutes. If the fluid findings and clinical picture warrant the diagnosis of acute poliomyelitis, 15 to 30 c.c. of serum are given immediately and very slowly intraspinally, and the needle is then withdrawn. This method saves time and a second lumbar puncture in positive cases. The patient is placed in a comfortable position and from 50 to 100 c.c. of serum are injected intravenously. The injections are repeated after twelve hours in severe cases. If the symptoms are aggravated and the respirations become irregular or rapid and shallow, another lumbar puncture should be made immediately and the excess of fluid withdrawn.

Results.—The results of several observers are suggestive, but Peabody[35] is inclined to believe that no good case is made out for serum. Since it is common knowledge that the virulence of outbreaks varies considerably, comparisons should be made only with untreated controls in the same epidemic.

Draper, who has had a wide experience in poliomyelitis, believes that a cell count in the spinal fluid above 100 forebodes the more serious type of the disease. In the author's series, there were several cases of this kind in which the cell count was high responding favorably to serum treatment. His results, when analyzed, show definitely that the progress of the disease is arrested in cases treated within forty-eight hours after the onset and with more than 50 c.c. of serum. He believes that the remainder of this series may serve as partial controls. These results were obtained in the severe epidemic of 1916, and in Vermont similar results were obtained by Edward Taylor.

GENERAL TREATMENT.—This is the same as that used in other acute infectious diseases. It should be remembered that constipation and retention frequently occur in these patients. The patients are often irritable, anxious and apprehensive, and suffer much pain. It is very important that the nurse should be gentle, sympathetic, and reassuring. A skillful nurse can add greatly to the comfort of the patient by relieving the strain from affected muscles; for example, high pillows increase the discomfort of the patient by stretching the neck. The author has seen patients who have not slept for two nights become quiet and go to sleep almost immediately after taking away a head pillow and supporting the shoulders slightly so that the neck could be arched backward. In cases with hyperesthesia, the affected part is protected by cotton and placed in a comfortable position.

Salts are preferable to castor oil as laxatives. For the pain, **morphia** is often required and the author has used it in cases of partial involvement of the respiratory centers to keep the patient perfectly quiet, thus decreasing the respiratory requirements.

DRUGS.—Hexamethylenamin has been recommended on the basis that formaldehyd is liberated in the spinal fluid, but the amount is so exceedingly small that little benefit can be expected. On account of the large number of cases having hematuria following the administration of this drug, the author has discontinued its use in poliomyelitis. Adrenalin has also been recommended but from his experiments on monkeys, the author believes that its use increases the severity of the disease.

TREATMENT OF PARALYSES.—**Complete rest of the affected muscles** has given the best results in the author's hands. The tension of the hamstrings, for example, is relieved by placing a **roll under the knees. Sand bags and an L-splint** protect a foot-drop. The bed covers should be supported on a frame, which can be conveniently made with half barrel hoops connected with three or four staves and the sharp edges covered with adhesive plaster.

Paralysis of the deltoid presents a difficult problem. The author has used a **counter-weighted sling** to advantage. After the patient is ambulant, a platform splint is placed in the axilla.

Warm salt water baths are beneficial after the febrile stage. Massage is contra-indicated until the hyperesthesia has disappeared and then should be instituted with caution. The author's practice is to make every attempt to keep the **muscle at rest** for at least **four weeks** after the acute stage. After this, **passive manipulation** is used gradually[36] until active motion (muscle training) can be instituted. This part of the treatment properly belongs to the orthopedic surgeon. The **foot of the bed should be elevated** when patients with paralyses of the pharyngeal muscles and those with respiratory involvement have an excess of mucus in the throat.

PREVENTION.—The use of convalescent human serum as a prophylactic measure is impractical because of the difficulty and expense involved. Since the susceptible rate is very low and there are no means of detecting the susceptible persons, the method is wasteful. Vaccination with altered or changed virus, as in the Pasteur treatment, has been tried experimentally in monkeys without success. Moreover there is an element of danger in such a method. It is apparent from epidemiological studies that the susceptibility decreases as the child grows older, so that the only promising method of prevention is **isolation until the age of relative nonsusceptibility arrives.**

Present ideas concerning the communicability of poliomyelitis are based on results obtained in studies of the experimental disease in monkeys. By reason of the parallelism of the human and experimental disease, both in their clinical and pathological aspects, it is believed that inferences drawn from experiments with monkeys may be accepted with a certain degree of safety as applicable to the solution of problems in connection with human cases. Indeed, there is perhaps no other experimental disease which so closely approaches the human analogue.

DISTRIBUTION OF THE VIRUS IN THE HOST.—As sources of material for studying the distribution of the virus in the host there are (*a*) autopsy material from human cases and monkeys; (*b*) body fluids obtained from the living human case; and (*c*) tissues from the monkey sacrificed at any stage of the experimental infection, and human tonsils and adenoids removed surgically.

(*a*) *Inoculations of material obtained at autopsy from the human case and the monkey demonstrate the virus in the following tissues:* (1) The brain[37] and cord, especially the medulla, basal ganglia, cervical and lumbar enlargements, posterior root ganglia,[38] and their cranial analogues;[39] (2) the sympathetic ganglia;[39] (3) nasal and pharyngeal mucosa,[40] and tonsils;[38] and (4) the lymph glands.[41]

The virus is not found in the cerebrospinal fluid,[38] blood,[42] or viscera,[43] postmortem.

(*b*) *Body Fluids.*—(1) *Cerebrospinal Fluid.*—The virus has not been found in the cerebrospinal fluid of the human case at any stage, but in certain experiments on the route of infection, using the monkey as the test animal, the virus was detected in the spinal fluid soon after intravenous injection and after nasal application.[44]

(2) *The Blood.*—The virus has not been found at any stage in the blood in human cases, though in the monkey, on the first day of symptoms, it has been detected in one instance when large amounts of blood were inoculated.[42] After intravenous injection of the virus into the blood, the virus tends to disappear, so that after 120 hours it is no longer present.[44]

(3) *Nasal Washing.*—Both human and monkey nasal washings contain the virus[45] during the acute stage, and in the latter it has been detected six days before the onset of poliomyelitis.[46] It is very much diminished in amount after the first week, but Lucas and Osgood report the presence of the virus in nasal secretions four months after a second attack.[47] The definite time of the complete disappearance of the virus has not been determined because of experimental difficulties.

(4) *Stools.*—The Swedish observers[45] believe that the virus leaves the body also by way of the intestinal tract. The criteria of the experimental disease which these observers employed do not correspond to

those actually accepted, so that there still remains some doubt as to the significance of their results.[46] The source of the virus in the stools is probably the swallowed mucus from the upper respiratory tract.

(*c*) *Tissues from Sacrificed Monkey, and Human Tonsils and Adenoids Removed Surgically.*—(1) The distribution of the virus in monkeys varies according to the route of injection and the time elapsing since the injection. Flexner and his co-workers have traced the course of the virus after nasal application through the nasal mucosa, into the olfactory lobes, the cerebrospinal fluid, later to the posterior root ganglia, and finally into the cord and medulla. Subsequently the virus disappears from the spinal fluid and overflows in small amounts into the blood. After intravenous injection, the virus may come through into the spinal fluid, and follow the usual course, provided the meningeal choroidal defense[48] has been overcome. Otherwise the virus tends to disappear from the blood and is anchored in the spleen, bone-marrow and lymph glands.

(2) Tonsils[49] and adenoids removed at autopsy from human cases contain the virus but it is rarely present in these tissues removed on the tenth day or later after the attack.[50]

(3) During the acute stage the virus is found regularly in the nasal mucosa of monkeys, but after seven days quickly disappears and is rarely found after the tenth day. Lucas and Osgood[51] report the detection of the virus in the nasal mucosa of monkeys five weeks and six and a half months, respectively, after the acute stage. This is to be regarded as exceptional.

However, it follows that a small number of human cases may harbor the virus over long periods.

Routes of Infection.—Once the virus is adapted to monkeys, only extremely small amounts are required to produce experimental poliomyelitis by the direct or cerebral route. For example, 0.001 c.c. of a Berkefeld filtrate of a 5 per cent. suspension of the central nervous system, *i. e.*, 1/500,000 gram of nervous tissue, often suffices.

Slightly larger doses are required by intraocular injection; still larger intraspinally, and large doses intraperitoneally. The virus travels easily in the perineural lymph spaces as shown by response to intrasciatic injection. Subcutaneously, the virus infects only with difficulty, and intravenously extremely large doses may fail. By the latter route infection may be brought about if an aseptic inflammation of the meninges has been provoked previously by the intraspinal injection of foreign protein. Microscopic examination shows a much more severe reaction than is usually found when other routes are employed.

Leiner and von Wiesner[52] have reported the production of experimental poliomyelitis by feeding the virus to monkeys after large doses of morphin had been given, though in the author's hands this method has failed even when the animals were given the virus every day for forty days. Incidentally, no immunity to intracerebral injection was effected by feeding.

With these facts in mind the natural mode of infection in the human being may be approached. The three possibilities, the nasal, the gastro-intestinal, and the subcutaneous or intravenous, will be discussed briefly in the reverse order. The last is apparently eliminated from consideration because of the large doses of the virus required to infect, and on account of the absence of positive data to support the view. The second, or stomachal route, has even less basis, in view of the extreme difficulty of producing the infection by this means. Furthermore, the virus is very sensitive to external influences and it is difficult to conceive of its ever reaching the host in quantities sufficient to infect by food, water, or milk supply.

The nasal route is now generally accepted.[50] The detection of the virus in nasal washings during the incubation period (human case), the ease of infection in the monkey, and the experiments already noted relating to the course of the virus from the nasal mucosa to the cord, all point towards this atrium of infection.

In brief, then, it appears that the virus is propagated in the central nervous tissues of the host, does not survive the external conditions of mediation, but by chance is transferred either directly or indirectly from nasal mucosa of the host to nasal mucosa of the susceptible new host. Because of the extreme difficulty of producing the infection by intravenous injection of very large amounts of the virus, it seems probable that the virus goes directly through the nasal mucosa to the olfactory lobes by means of the perineural lymph spaces, and not first into the circulation and then into the meninges.

Mechanisms of Defense.—The virus, having been transferred to the nasal mucosa of the second human being, may lodge therein, remain active (there are no indications that it multiplies), or it may be destroyed. That the latter may happen is shown by experiments on the neutralization of virus by nasal washings.[53] In general, the nasal washings of healthy adults, but not of all children, neutralize the virus. This power of the nasal secretions to neutralize may, therefore, be regarded as the first line of defense of the human body against the entrance of the virus, and if this were the only line of defense, infection or non-infection would be a relatively simple matter. However, there are other obstacles in the way of the virus, so that if the neutralizing power is absent from the nasal secretions, infection may not always result, but the person on whose nasal mucosa the virus falls becomes the carrier. Flexner, Clark and Fraser[54] have detected the virus of poliomyelitis in healthy adults, who never showed signs of infection, and the Swedish observers[45] believe that carriage is quite common.

Reference has already been made to the fact that large doses of the virus given intravenously rarely cause infection. If, however, an aseptic inflammation has been provoked in the meninges by the injection of foreign protein intraspinally, much smaller doses intravenously injected are allowed to pass through into the spinal fluid and cause experimental poliomyelitis.[48]

Whether this mechanism of defense operates in the human being can be surmised only. The experiment in the monkey is so definite that this method is employed in making *in vivo* neutralization tests of serums for antibodies active against the poliomyelitis virus.[55]

A third mechanism of a decisive nature is the presence of immune bodies in the serum, as shown by neutralization tests. Anderson and Frost[56] noted the presence of immune bodies in the serum of 66 per cent. of the persons who had been in close contact with poliomyelitis cases but who had not contracted the disease. They suggest the possibility that persons in contact with acute cases may become actively immune.

There are two other factors which may play a supportive rôle in deciding susceptibility or nonsusceptibility: the first is based upon the power of large doses of x-rays to increase the susceptibility of the monkey to experimental poliomyelitis;[57] and secondly Zingher[58] has observed a positive Schick test in poliomyelitic children to be twice the expected rate for the same ages among the general population. The last two factors may be regarded as suggestive of minor influences in determining infection or noninfection, once the virus has passed the first barrier.

Since the various defensive measures described above are non-related, the chances of a combination-allowing infection, supposing an active virus to be present, would be a function of the percentage product of the three major factors. No data have been collected on the relative occurrence of any of these factors in samples of population, but it is reasonable to suppose that eventually the low susceptibility rate may be better understood. In the large epidemic of 1916 the virus had abundant opportunity for general distribution, and it is conceivable that the majority of persons in the areas of dense population were exposed. Yet the attack rate on New York City[11] was only 1.59 per thousand of the total population. Of all the cases 97 per cent. occurred in persons under the age of sixteen. The attack rate per 1,000 population under 10 years was 18, and among those over 10 was 0.23.

CARRIERS.—The definite seasonal distribution of poliomyelitis, with some exception, and the experimental data supporting the view that the virus does not survive long outside the host, suggest the recovered case or the carrier as the interepidemic reservoir of the virus. The rapid disappearance of the virus from the nasopharynx as the acute stage passes, and its coincidence with the development of immune bodies in the blood, controverts the idea that the recovered case harbors the virus during the interim. However, the observation of Lucas and Osgood, *viz.*, finding the virus in the nasopharynx of the monkey five weeks and six and a half months after onset, is not to be disregarded. In experiments with monkeys, we have shown that the virus applied to the nasal mucosa of monkeys which have been passively immunized quickly disappears without causing experimental poliomyelitis, whereas in the normal monkey, the virus persists. Therefore, all things considered, it seems that the virus has a greater chance of surviving in the nasal secretions of the carrier than in the recovered case. In the former there are only local agencies for combating the virus, whereas in the latter all the agencies of the body may react for defense. In spite of the very obvious experimental difficulties the virus has been detected in the nasal mucus of healthy contacts.

COMMUNICABILITY.—The virus of poliomyelitis enters the central nervous system by way of the nasopharynx, multiplies, and leaves the body by the same route. In the recovered cases the virus probably disappears, except in rare instances, within ten days to two weeks after the acute attack. The duration of carriage of the virus by healthy contacts has not been determined.

Field observations lead the author to believe that only slight contact between the carrier of the virus (case, healthy carrier, or person in the incubation period) and the *susceptible* person suffices for the transfer of the virus. In this respect, and also in the fact that the virus is present in the nasal washings of the person at least six days before onset, poliomyelitis resembles measles.

The stage of communicability, then, is from six days before to ten days after the onset—roughly speaking, from one week before to two weeks after. This presents difficulties from the standpoint of prevention.

ISOLATION.—In Vermont the State Board of Health has adopted the following plan with apparent success: **The patient and intimate contacts are quarantined for three weeks.** A search is made for all persons, especially children, who have been associated with the patient for the previous week. These families are then visited by a representative who discusses the danger of repeated exposure. Thus children who may be in the incubation period are voluntarily quarantined for two weeks.

The efficiency of quarantine varies inversely as the duration: it is suggested as a practical measure that the period of isolation for cases and contacts be reduced to seventeen days from onset.

INDIVIDUAL PROPHYLAXIS.—During an epidemic, **travel and visiting should be limited to absolute necessity.** The breadwinner should keep away as much as possible from other members of the family, especially children, and should observe the rules of good respiratory manners.

Various antiseptics, as nasal douches, have been recommended as preventatives. Experiments with monkeys have shown that these measures not only possess no value in prevention but actually increase the liability to infection. It has been found that rinsing with **isotonic salt solution** mechanically removes the bulk of the virus in carriers and promotes the neutralizing power of the nasal secretions. It should be remembered that some risk of antrum and sinus infection attends such procedures. It is very important that the head should be kept in the anteroposterior vertical plane and inclined slightly forward. Instructions to the laity to prepare the solutions daily by adding a teaspoonful of salt to a pint and one-half of water and boil down to one pint volume insures sterility.

INSTRUCTION DURING EPIDEMIC PERIODS.—The organization of public health forces during epidemics is a function of the State Boards of Health. In addition to the usual program of combating an epidemic with an organized corps of diagnosticians, nurses, epidemiologists, and social workers, the author has found that it is of great advantage to put into operation a plan of education.

The first group to receive instruction are local health officers, the next the physicians, and finally talks are made to the public, usually in the high school auditorium. Following such a plan, it is the author's experience that much more can be accomplished in the early diagnosis, treatment, and isolation. The coöperation of the public is obviously necessary, and depends for the most part upon the efforts of the practicing physician.

Prognosis.—The mortality in the 1916 epidemic in New York City was 27 per cent. The highest mortality was observed among children under one year (43 per cent.). Among all cases under 5, and those under 10 years, the mortality was practically the same (27 per cent.), and among those over 10 years 31 per cent. The mortality among sporadic cases is very much less. In Vermont the mortality is from 15 to 25 per cent. It is always highest in adults. Reports of epidemics since 1916 show that the mortality is much less; for example, among 259 cases of the Davenport (1917) and Dubuque (1918) epidemics reported by Rosenow,[28] the mortality was only 7.3 per cent. Residual paralyses were less in this outbreak than in the New York or Swedish epidemics. In general, residual paralysis may be expected in from 25 to 45 per cent. of all cases.

In the individual cases, a prognosis cannot be made until the febrile period has passed. In cases with respiratory paralysis the outlook is always serious. There is hope in the fact that completely paralyzed muscles may recover partially, sometimes completely, but much depends upon the after-care.

Draper believes that the number of cells present in the spinal fluid during the first twenty-four hours is of prognostic significance. He claims that cases in which the count is under 100 per cubic millimeter rarely develop paralysis, while from 200 to 500 cells forebode paralysis, and in those in which the count is from 700 to 1,000 cells, the prognosis for life is unfavorable. In the author's experience, there have been many exceptions to this generalization.

Historical.—In a treatise on "Diseases of Children" (Philadelphia, 1793), Michael Underwood mentions the occurrence of paralysis in children following a brief illness. And Badham in the London Medical Gazette, 1835, describes a few cases of paralysis following an acute onset. In 1840 Heine of Stuttgart separated from a heterogeneous group of paralyses a clincal type characterized by cord lesions and referred to at that time as cases of infantile paralysis. A quarter century later Prévost and Vulpian studied the lesions in the anterior horn and attributed to them the symptoms of infantile paralysis. Charcot in 1881 in his lectures on nervous diseases described the acute onset preceding the paralysis. Strümpell (1884) presented several cases of acute brain disease and pointed out the epidemiological occurrence, and drew the analogy between them and poliomyelitis, the infectious nature of which he emphasized. This conception was not concurred in generally and awaited entirely new data before being accepted. Meanwhile Kussmaul had become impressed with the lesion in the grey matter and suggested the name poliomyelitis (polios—grey) for the disease. Medin (1889) whose name is connected with Heine's in the designation of poliomyelitis (Heine-Medin disease) reported a large Swedish epidemic and accurately described the acute stage. Wickman, a pupil of Medin's, studied these Swedish epidemics, including the great epidemic of 1904. His pathological, clinical, and epidemiological contributions are classic. The development of the pathology of acute poliomyelitis rests upon the work of Harbitz and Scheel (1907).

The first epidemic (11 cases) was reported by Colmer of Louisiana. Three other outbreaks were described before 1885 and since that time the disease has appeared in epidemic form in some part of the world every year. The first large epidemic in America occurred in Vermont in 1894 (132 cases) and was reported by Caverly, who first called attention to a small number of cases (6), apparently of the same disease, but which did not reach the paralytic stage. The disease has been endemic in Vermont with epidemic outbreaks since that time. Wickman later and independently described this type as "abortive" cases.

New York City was visited by a large outbreak (2,500 cases) in 1907 and again in 1916 (9,005 cases). In Wisconsin there were about 1,000 cases in 1908, and in the same year there was a small outbreak in Minnesota (150 cases). In 1909 Minnesota suffered more severely (1,100 cases) and again in 1910 (1,000 cases). In the Nebraska outbreak of 1909 there were 999 cases. The 1914 outbreak in Vermont resulted in 300 cases among about 300,000 population. Every state in the Union has been visited by poliomyelitis in the last 15 years, and it is to be presumed therefore that the virus is widely distributed over the country at present.

Recent progress in studies on poliomyelitis are based upon the transmission experiments of Landsteiner and Popper, Straus and Huntoon, and Flexner and Lewis, all in 1909. The last observers were able to reproduce the experimental disease in monkeys by injecting a suspension of poliomyelitic nervous tissue directly into the brain and by the same method successfully transferred the disease from monkey to monkey through many passages. Reference to these experiments will be found in the text.

References

1. Caverly, C. S. Medical Record, New York, 1894, xlvi, 673.
2. Wickman, I. Beiträge zur Kenntnis der Heine Medinschen Krankheit, Berlin, S. Karger, 1907; also Die Akute Poliomyelitis, Berlin. Julius Springer, 1911. (English Trans. by J. W. Maloney, Nervous and Mental Disease Monograph Series, No. 16, The Journal of Nervous & Mental Diseases Pub. Co., New York, 1913.)
3. Draper, G. Vol. II, Nelson's Loose-Leaf System of Medicine, Thomas Nelson & Sons, New York City.
4. Report of Committee on Special Investigation of Poliomyelitis, Dept. of Health, City of New York, 1916.
5. Landsteiner, K., and Popper, E. Ztschr. f. Immun., Orig., 1909, ii, 377.
6. Strauss, I., and Huntoon, F. M. N. Y. Med. Journ., 1910, xci, 64.
7. Flexner, S., and Lewis, P. A. Jour. Amer. Med. Assoc., 1909, liii, 1639.

8. Flexner, S., and Noguchi, H. Jour. Amer. Med. Assoc., 1913, lx, 362; and Jour. Exper. Med., 1913, xviii, 461.
9. Flexner, S., Noguchi, H., and Amoss, H. L. Jour. Exper. Med., 1915, xxi, 91.
10. Smillie, W. G. Jour. Exper. Med., 1918, xxvii, 319.
11. Amoss, H. L. Jour. Exper. Med., 1914, xix, 212.
12. Amoss, H. L. Jour. Exper. Med., 1917, xxv, 545.
13. Mathers, G. Jour. Amer. Med. Assoc., 1916, lxvii, 1019; Jour. Infec. Dis., 1917, xx, 113. Rosenow, E. C., Towne, E. B., and Wheeler, G. W. Jour. Amer. Med. Assoc., 1916, lxvii, 1202; *ibid.*, 1917, lxviii, 280. Nusum, J. W., and Hersog, M. Jour. Amer. Med. Assoc., 1916, lxvii, 1205; 1916, lxvii, 1437; 1917, lxviii, 24.
14. Bull, C. G. Jour. Exper. Med., 1917, xxv, 557.
15. Flexner, S., Peabody, F. W., and Draper, G. Jour. Amer. Med. Assoc., 1912, lviii, 109.
16. Mueller, E. Die Spinale Kinderlähmung, Julius Springer, Berlin, 1910.
17. La Fetra, L. E. Arch. Pediat., 1909, xxvi, 328.
18. Gay, F. P., and Lucas, W. P. Arch. Int. Med., 1910, vi, 330.
19. Peabody, F. W., Draper, G., and Dochez, A. R. Monograph No. 4, Rockefeller Institute, New York, 1912, 97.
20. Taylor, H. D. Jour. Exper. Med., 1919, xxix, 97.
21. Taken from article on Maladie de Heine-Medin by Ch. Dopter, Vol. iv, Nouveau Traité de Médecine, Paris, 1922.
22. Reegan, J. C. Arch. Ped., 1920, xxxvii, 257.
23. Lovett, R. W., and Sheppard, P. A. E. Bull. Mass. State Bd. of Health, 1910.
24. Thomas, H. M. Made by Wilms Co., Baltimore, Maryland.
25. Noguchi, H. Serum diagnosis of syphilis. Ed. 3, J. B. Lippincott Co., Philadelphia and London, 1912.
26. Amoss, H. L. Jour. Amer. Med. Assoc., 1919, lxxii, 1289.
27. Noguchi, H. Jour. Amer. Med. Assoc., 1921, lxxvii, 632.
28. Rosenow, E. C. Jour. Amer. Med. Assoc., 1921, lxxvii, 588.
29. Römer and Josephs. München. med. Wochenschr., 1910, lvii, 568.
30. Flexner, S., and Lewis, P. A. Jour. Amer. Med. Assoc., 1910, liv, 1780.
31. Netter, A., Gendron, A., and Touraine. Compt. rend. Soc. Biol., 1911, lxx, 625.
32. Amoss, H. L., and Chesney, A. M. Jour. Exper. Med., 1917, xxv, 581.
33. Flexner, S., and Amoss, H. L. Jour. Exper. Med., 1917, xxv, 499.
34. Amoss, H. L., and Eberson, F. Jour. Exper. Med., 1919, xxix, 597.
35. Peabody, F. W. Bost. Med. and Surg. Jour., 1921, clxxxv, 174.
36. Lovett, R. W. Jour. Amer. Med. Assoc., 1922, lxxviii, 1607; and The treatment of infantile paralysis. P. Blackiston's Sons & Co., Philadelphia, Pa., Second Edition.
37. Flexner, S., and Lewis, P. A. Jour. Amer. Med. Assoc., 1909, liii, 1639.
38. Flexner, S., and Clark, P. F. Jour. Amer. Med. Assoc., 1911, lvii, 1685.
39. Flexner, S., Clark, P. F., and Amoss, H. L. Jour. Exper. Med., 1914, xix, 205.
40. Flexner, S., and Lewis, P. A. Jour. Amer. Med. Assoc., 1910, liv, 535.
41. Flexner, S., and Lewis, P. A. Jour. Amer. Med. Assoc., 1910, liv, 1140.
42. Clark, P. F., Fraser, F. R., and Amoss, H. L. Jour. Exper. Med., 1914, xix, 223.
43. Flexner, S. Jour. Amer. Med. Assoc., 1912, lix, 15.
44. Flexner, S., and Amoss, H. L. Jour. Exper. Med., 1914, xx, 249.
45. Kling, C., Petterson, A., and Wernstedt, W. Communicat de l'Inst. Med. de l'Etat à Stockholm, 1912, iii, 5.
46. Taylor, E., and Amoss, H. L. Jour. Exper. Med., 1917, xxvi, 745.
47. Lucas, W. P., and Osgood, R. B. Jour. Amer. Med. Assoc., 1913, lx, 1511.
48. Flexner, S., and Amoss, H. L. Jour. Exper. Med., 1917, xxv, 525.
49. Landsteiner, Levaditi and Pastia. Semaine médicale, 1911, xxv, 296.
50. Flexner, S., and Amoss, H. L. Jour. Exper. Med., 1919, xxix, 379.
51. Osgood, R. B., and Lucas, W. P. Jour. Amer. Med. Assoc., 1911, lvi, 495.
52. Leiner and von Wiesner. Wien. med. Wochenschr., 1910, xxiii, 2482.
53. Amoss, H. L., and Taylor, E. Jour. Exper. Med., 1917, xxv, 507.
54. Flexner, S., Clark, P. F., and Fraser, F. R. Jour. Amer. Med. Assoc., 1913, lx, 3.
55. Amoss, H. L., and Eberson, F. Jour. Exper. Med., 1918, xxvii, 309.
56. Anderson, J. F., and Frost, W. H. Jour. Amer. Med. Assoc., 1911, lvi, 663.
57. Amoss, H. L., Taylor, H. D., and Witherbee, W. D. Jour. Exper. Med., 1919, xxix, 115.
58. Zingher, A. Dept. Health, City of New York, Reprint Ser. 52, 1917.

CHAPTER LI

TUBERCULOSIS OF THE GENITO-URINARY SYSTEM

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Introduction, p. 361; Etiology, p. 362:—Active cause, p. 362; Predisposing causes, p. 362; Avenues by which tuberculosis reaches the genito-urinary system, p. 362.
Tuberculosis of the kidney and ureter, p. 364:—Incidence, p. 364; Symptomatology, p. 365; Diagnosis, p. 367; Course and prognosis, p. 371; Treatment, p. 372; Pathology, p. 374.
Tuberculosis of the bladder, p. 376:—Etiology, p. 376; Symptomatology, p. 377; Diagnosis, p. 379; Treatment, p. 379; Prognosis, p. 380; Pathology, p. 380.
Tuberculosis of the epididymis, testicle, seminal vesicles, prostate, urethra and penis (genital tuberculosis), p. 381:—Introduction, p. 381; Etiology, p. 381.
Tuberculosis of the prostate, p. 383:—Pathogenesis, p. 383; Symptoms and diagnosis, p. 383; Treatment, p. 383; Prognosis, p. 383.
Tuberculosis of seminal vesicles, p. 383:—Symptoms and diagnosis, p. 384; Treatment, p. 384; Prognosis, p. 384; Pathology, p. 384.
Tuberculosis of the testicle and epididymis, p. 384:—Pathogenesis, p. 384; Symptoms and diagnosis, p. 385; Treatment, p. 385; Prognosis, p. 386.
Tuberculosis of the urethra, p. 387:—Symptoms and diagnosis, p. 387; Treatment, p. 387.
Tuberculosis of the glans penis, p. 387:—Symptoms, p. 387; Diagnosis, p. 387; Treatment, p. 387.

GENITO-URINARY TUBERCULOSIS

Introduction.—Modern methods of urological diagnosis have shown not only the great interest but the great importance of tuberculosis of the genito-urinary system. While it is not as often encountered as other forms of tuberculosis, *e. g.*, tuberculosis of the lungs, glands, bone, etc., it is common enough to demand eternal vigilance on the part of the practitioner in the hope of its early recognition and treatment. Too often tuberculosis of the kidney goes unrecognized for months or even years, with the result that a unilateral affection is allowed to become bilateral, and the prognosis altered from a favorable to a hopeless one, or a descending bladder tuberculosis develops with its resulting misery. Tuberculosis of the genito-urninary system is seldom primary, but it is practically always secondary to some focus elsewhere in the body, such as the lungs, glands, bone, etc. The term primary tuberculosis of the genito-urinary system is employed and is used to denote the organ of the genito-urinary tract to become first involved, without consideration of any other organ or system of the body. For example, if the kidney, following an already existing active or latent pulmonary tuberculosis, became involved in the tubercular process, and the urine laden with tubercle bacilli descended the ureter and caused a bladder tuberculosis, we would describe the condition as a primary tuberculosis of the kidney, and the bladder as a secondary tuberculosis of the bladder. Renal tuberculosis, however, can take place without there being any discoverable lesion elsewhere in the body, and the condition would also then be primary as far as the whole body was concerned. As mentioned above, this hardly ever occurs.

Any part of the genito-urinary system may be invaded and the different organs of the system may be attacked so rapidly that if one has not had the opportunity of observing the case from its incipiency, he would be unable to state which was the primary organ and which the secondary organ involved. Also, one or more of the various organs may be attacked at the same time. The kidney, however, is by far the commonest organ to be primarily involved. It may become involved following years of latency of the disease in some other part of the body, and it itself may exist for decades without producing any active signs or symptoms indicating its existence; or it may be discovered accidentally at the autopsy table or following a careful study for some other affection.

For example, in the year 1922, the author had a patient autopsied following death from miliary tuberculosis, complicating a tuberculous condition of the epididymis, and found his right kidney entirely destroyed by an advanced tuberculous condition. During life, the patient gave no history at all suggestive of renal tuberculosis and voided perfectly clear urine. This absence of symptoms was caused by autonephrectomy about which more will be said later.

Etiology.—ACTIVE CAUSE.—The active cause is the tubercle bacillus.

PREDISPOSING CAUSES.—It is a well-known and well-established fact that tubercle bacilli may gain access to the body and be excreted by the kidneys without producing renal lesions. Just why in some cases they should be arrested and cause lesions indicating renal involvement may be impossible of explanation. Various predisposing causes, however, may be present at times and account at least theoretically for the occurrence of the affection.

These are (1) hereditary predisposition; (2) trauma; (3) calculous or calcareous disease; (4) gonorrheal infection; (5) syphilis; (6) abnormal mobility (ptosis); and (7) congenital malformations.

None of these predisposing causes, however, are present in the majority of the patients suffering with urogenital tuberculosis.

AVENUES BY WHICH TUBERCULOSIS REACHES THE GENITO-URINARY SYSTEM.—Infection of the genito-urinary tract may occur in various ways: (1) By hereditary transmission; (2) hematogenous infection; (3) lymphatic infection; (4) direct extension; and (5) by infection from without.

Hereditary Transmission.—Tuberculosis has been met in the fetus. While ordinarily tuberculosis is not transmitted hereditarily as was once thought usual, nevertheless its possibility is unquestioned, because tuberculosis has been found in the fetus. In the latter cases, direct transmission of the disease from the parents must be admitted.

Hematogenous Infection.—By far the vast majority of cases of tuberculosis of the genito-urinary system are blood borne. The presence and recoverability of tubercle bacilli in the blood of individuals suffering with tuberculosis is a well-established fact. Further, evidence that tubercle bacilli in active tuberculous subjects are constantly being filtered through the kidneys is well known, and during these passages if the kidney tissue is resistant, no harm results, whereas if the kidney constitutes a "locus minoris resistantiæ," the bacilli may gain a foothold resulting in a diseased or pathological condition of the organ.

Lymphatic Infection.—It is only of late years that the importance of lymphatic extension in kidney infections has been sufficiently well recognized. While it is not as common as the hematogenous method of extension, it certainly does occur and affords the only explanation for the types of renal tuberculosis where the major, primary or only lesions are noted in the pelvis of the kidney or along the portion of the renal papilla which projects in the kidney, the remainder of the kidney being free of the condition. Brongerma is a strong advocate of the lymphatic mode of extension and believes that the infection takes place from the mediastinal glands in pulmonary tuberculosis. He has by autopsy studies shown tuberculosis of the apex of the lung, with tuberculosis of the glands, extending along the aorta through the diaphragm to the neighborhood of the kidney on the same side. In this way, he accounts for the renal tuberculosis which in the vast majority of cases is unilateral in its early stages. The upward extension of a tuberculous process in the bladder to the kidney (ascending infection) by way of the ureter at one time was thought to be not uncommon. It is now proven that it is practically impossible for the tubercle bacilli to travel upwards from the bladder to the kidney against the urinary current unless an abnormality of the ureterovesical valve exists, and that when evidence exists of a tuberculous infection in a bladder ascending upward to the kidney, it does so through the lymphatics in the walls of the ureter. It has been definitely shown that there is a direct connection through the lymphatic system between the kidney pelvis, ureter, bladder and posterior urethra.

Direct Extension.—The direct extension of a tuberculous process from some neighboring organ to organs of the genito-urinary system is a well-known fact. The organs which may be involved and lead to extension in the genito-urinary tract are the peritoneum, intestines, rectum, spine (caries), adrenal gland, etc. The occurrence of the extension in this manner is easily recognized by a sclero-tuberculous mass binding the two organs and readily distinguishing it from the other types.

Infection from Without.—Whether tuberculosis may result through sexual intercourse, the bacilli from a tuberculous man projected in the vagina giving rise to the disease in the female is still a disputed question. If it occurs at all, it certainly must be extremely rare.

To recapitulate, in the vast majority of cases of tuberculosis of the genito-urinary system the infection is most often hematogenous in origin; occasionally the route is through the lymphatics, occasionally the avenue may be by direct extension and practically never by hereditary transmission or sexual intercourse.

TUBERCULOSIS OF THE KIDNEY AND URETER

By renal tuberculosis is meant the lodgment of the tubercle bacillus within the substance of the kidney resulting in the production therein of pathological changes. Tuberculosis of the kidney may be of the acute or chronic form, the former being a part of a rapidly fatal acute general miliary tuberculosis and possessing, therefore, nothing of special interest. The second or chronic form is the insidious type most frequently encountered and possesses special interest to the practitioner on account of the frequency with which it is recognized by careful examination, thereby allowing proper treatment to be instituted, with the result of not only saving the patient's life, but saving him from a life of misery (*See* BLADDER TUBERCULOSIS). As has been already stated it is practically always secondary to some focus elsewhere in the body, as the lungs, glands, joints, etc. In two-thirds of the autopsies of patients dying of renal tuberculosis, active or latent lesions are demonstrated in the lungs, mediastinal or mesenteric glands. In the male it is very frequently associated with similar lesions in the genital tract. In 258 cases of genital tuberculosis reported by Barney and Keys, 38 were associated with renal lesions; in 22 patients renal lesions were diagnosed after the development of the disease in the prostate and epididymis, and in 16 the renal condition was primary.

Incidence.—*Age.*—Like tuberculosis elsewhere in the body, renal tuberculosis is essentially a disease of young adult life and is most common between the ages of 20 and 40. Practically all statistics are in agreement on this point. In Walker's analysis of 373 cases, the average age of the patients was 27.66 years, and that the largest number among those was in the decade from 20 to 30 years. In Wildbolz's series of 315 cases, 224 were within the ages of 20 to 40 years. In Asakura's cases, 60 were within the same decades.

SEX.—There is not the same agreement regarding frequency of the disease in the male and female. Most statistics cite the greater frequency of the disease in the male. In a series of 1,176 cases reported by Von Frisch, Wildbolz, Asakura, Walker, Guillard, Tuffin, Albarran and Braasch, there were 633 males and 543 females. The relative percentage in the females may be increased by the fact that the diagnosis in the female is easier, on which account a relatively greater number of women are operated upon.

UNILATERAL AND BILATERAL RENAL INFECTION.—The disease may be unilateral or bilateral. In the vast majority of cases, the disease in the beginning is unilateral, with a great tendency for the disease later to become bilateral. In children the bilateral lesions are seen more often than the unilateral. Halle and Motz found in 131 cases of renal and ureteral tuberculosis examined by them postmortem that the tuberculous lesions were unilateral in 89 and bilateral in 42. Bevan quotes the postmortem findings in 13,000 autopsies of all kinds done at Kiel. In this series 36.7 per cent. of all the tuberculous renal infections were unilateral. Since the advent of modern urological diagnostic methods enabling us by means of ureter catheterization to study the urines from each kidney separately, ample clinical evidence is obtainable proving the correctness of the view, that in from 60 to 80 per cent. of the cases, renal tuberculosis is unilateral when first seen.

The practical importance of this information is obvious. The incidence of genito-urinary tuberculosis can be best studied from the large mass of statistics gathered in 1913 by Hesse. In 10,664 autopsies, genito-urinary lesions were found in 2.13 per cent. Krzywicki in 1888 found 5 per cent. involvement of the genito-urinary organs in 500 autopsies performed on tuberculous subjects. Reclus in 1876 reported 12.8 per cent. in his series, and in 1911 Fowler and Godlee found 5.27 per cent. involvement of the genito-urinary organs. These figures apply almost entirely to adults. In children the percentage is very much lower. In Ritters' series of 5,000 tubercular children, only 14 showed evidence of genito-urinary involvement. Figures reported by others confirm the correctness of Ritters' findings.

Symptomatology.—A tuberculous process in the kidney even of an advanced nature may exist for months or even years without causing symptoms. As long as the focus remains confined to the kidney no symptoms are produced. It is only when lesions ulcerate and the infected tuberculous material gains access to the pelvis and ureter that symptoms develop. In the beginning, the symptoms are due to the irritation of the infected urine upon the pelvic, ureteral, and bladder mucosa. Later these structures become involved in the pathological process and symptoms due to inherent disease in them develop. The symptoms and signs are *local* and *general.*

Local Symptoms and Signs.—The first symptom which usually attracts the patient's notice is *vesical irritability.* This shows itself first in increasing frequency of micturition in the day. Later the patient will be compelled to get up at night one or more times. Urgency also develops. These symptoms gradually increase in intensity until a time arrives when the patient will be compelled to void every hour or two during the day and night. In the most marked cases, the frequency of urination is so marked that it most amounts to incontinence. Incontinence at night may be a symptom. In children, incontinence and enuresis may be associated. The urination is associated with a burning sensation along the course of the urethra, or the pain may be felt only in the prostatic urethra, perineum, or supra-pubic region. The pain at times is most intense at the end of urination, when muscular contraction takes place to expel the last few drops of urine. These cases are usually diagnosed and treated sometimes for months as cystitis. It cannot be too much emphasized that a primary cystitis is rare in the absence of the common casual factors of cystitis, such a gonorrhea, prostatic hypertrophy, stricture, etc.

Hematuria.—There is nothing characteristic about the hematuria of renal tuberculosis. It occasionally is a very early symptom, but may be so slight and brief that it is overlooked. At times, it may be very severe and demand operative relief. When severe, it is apt to be transient and lull the physician and patient into a false sense of security, when, as a matter of fact, the real danger has just begun. The most careful examination at this time, including all the diagnostic aids at the command of the modern urologist may fail to diagnose the condition. This type is apt to be diagnosed as "essential" renal hematuria. It is evident, that if a small tuberculous focus in proximity to some renal blood-vessel should ulcerate through it, severe hemorrhage might result, and the most exhaustive examination fail to determine it. The hematuria may recur at any time and without any provocative factor. A long time may elapse between the time of the initial bleeding and the development of other symptoms. It is related of one of our American surgical masters, whose memory we all revere, that twenty-five years before his death he had one sharp attack of hematuria and no subsequent urinary symptoms. Autopsy, in his case, revealed an old, healed tuberculous kidney. While, as stated above, there is nothing characteristic about the hematuria of renal tuberculosis, it is well to remember that, barring the exception, the hematuria is not severe, like that observed in renal tumor, nor associated with colic or constant pain, as in kidney stone.

Renal Pain.—This is a variable symptom. A patient may have a tuberculous kidney go on to complete destruction without even experiencing the least pain. About one-third of the cases develop some pain either in the loin or in the costo-vertebral angle region. It is usually of a dull aching character. Occasionally, if obstruction occurs from the passage of blood clots or inspissated masses, symptoms simulating renal colic may be produced. The author has had one case where the patient with only one kidney had it blocked by thick, inspissated pus, and as a result suffered from pain and anuria for several days. It was relieved by the simple passage of a ureter catheter. Another cause of severe pain in these patients is a tuberculous stricture of the ureter. The author once had a patient referred to him with symptoms of the most agonizing colic on the right side. Kidney stone was suspected. Study of this case showed that the patient had an absent left kidney, and that the colic in the right side was due to a tuberculous stricture of the ureter, secondary to a tuberculous condition of the only kidney. With a very cloudy urine from pus and the most violent colicky pains, only very careful study saved him not only from operation but probably death. Following ureter dilation, the patient not only never had another colic, but his urine cleared remarkably and his general health became normal. Mixed infection, pyonephrosis, perinephritic abscess, etc., will cause symptoms characteristic of these conditions from whatever cause.

Referred Pain.—Pain on the opposite side of the diseased kidney may be present. This can be due to a focus, like, for example, a right tuberculosis of the seminal vesicle, causing referred pain in the right loin, while the patient at the same time has a left kidney tuberculosis. At times the pain in the opposite side may be inexplicable. For example, a female patient of the author with severe pain in her right loin had a right kidney which was not only normal but which had undergone compensatory hypertrophy. Study and operation showed her left kidney to be destroyed by tuberculosis. The severe pain on the normal side and absence of symptoms from the diseased kidney caused one colleague to suggest that the author had crossed his ureter catheters during the examination.

Renal Tumor.—A tuberculous kidney seldom enlarges sufficiently to cause a tumor formation. When it occurs, it is usually due to a pyonephrosis or a perinephritic abscess.

GENERAL SYMPTOMS.—From what has already been said in the foregoing, it is evident that tuberculosis of the kidney may exist for years, without producing any systemic or constitutional symptoms. In the majority of instances, however, careful inquiry will elicit the information that for some time the patient has been below par, that he has been suffering with malaise, irritability, nervousness, insomnia, flushings, etc. These symptoms many times will be diagnosed as influenza, etc., and treated as such. As the disease advances, these symptoms will become aggravated and loss of weight will be noticed. A rise of temperature becomes a constant feature. It seldom goes beyond 100° to 101° F. (36.66° to 38.33° C.) unless mixed infection supervenes, when the temperature may reach a point of 103° F. (39.44° C.) or higher. An increase in pulse rate due to the toxemia will be noted. In the latter stages, prostration, and finally death from uremia supervene if both kidneys are involved.

REMISSION OF SYMPTOMS.—As is characteristic of tuberculosis elsewhere in the body, tuberculosis of the genito-urinary system may undergo marked remission in symptoms. The patient may gain in weight, his temperature reach and stay around normal, the symptoms ameliorate and the urine show considerable improvement.

Diagnosis.—Many factors are to be considered in the diagnosis of tuberculosis of the kidney. Of them all, the only certain one is the finding of the tubercle bacillus in the urine from the affected kidney. The means of diagnosis are the following: Urinary signs; animal inoculation; cultural methods; x-ray; cystoscopy and ureter catheterization; tuberculin tests; general physical examination and history; and operative interference.

URINARY SIGNS.—The typical appearance of the urine in renal tuberculosis is pale and cloudy from admixed pus which settles on standing and leaves a clear urine above. In the early stages the frequency of urination is due to both irritation and polyuria. Early polyuria is rather characteristic of tuberculosis and should cause one to be on the alert. The urine is acid. Most infected urines are alkaline due to ammoniogenic cocci. Acid pyuria should, therefore, lead one to suspect tuberculosis. Alkaline urine, however, due to mixed infection with ammoniogenic cocci, may be present in renal tuberculosis. Albuminuria is a constant feature. It may be due to the pus present, or to the toxic nephritis in either the healthy or tuberculous kidney. Albuminuria without inflammation may be noted in the urine of patients who have tuberculous lesions in the body elsewhere than in the genito-urinary system. Blood-cells, at least in microscopic amounts, will be found practically always. Tube casts are the exception rather than the rule. A point of great practical importance is the absence of bacteria after examination by the ordinary staining methods. This point cannot be too much emphasized. A teaching axiom that the author employs with his students is the following: Pus in the urine without demonstrable organisms by the ordinary staining methods means either tuberculosis or gonorrhea. Very often the latter disease can be eliminated, leaving tuberculosis as the only diagnosis. Quite a few times he has been able to make a supposedly keen diagnosis on this feature alone. Of course, if mixed infection with the colon bacillus or the various cocci supervenes, this diagnostic feature fails us. At the same time, we must not let the presence of the above organisms lead us away from the fundamental diagnosis of tuberculosis, as can easily happen. The greatest clincher however, in the diagnosis is the demonstration of the tubercle bacillus in the urine associated with pyuria.

Tubercle Bacillus in the Urine.—The finding of the tubercle bacillus in the urine unassociated with pus is not sufficient for a diagnosis of tuberculosis, as from what has been said before, pulmonary tuberculosis patients may eliminate tubercle bacilli in the urine without there being present any pathological lesions in the kidney. A point of the greatest practical importance is the need of avoiding confusion of the tubercle bacillus with the smegma bacillus.. As has been shown by Young and Churchman, the smegma and tubercle bacillus are morphologically and tinctorially identical. Furthermore, the smegma bacillus is not only a normal inhabitant of the external genitals, especially the glans in the male, but may be found in the anterior urethra down as far as the external sphincter. The author has seen this error made in at least one case. This being the case, the only way is the exclusion of the smegma bacillus as a contaminating factor by not only fully scrubbing the external genitals with soap and water and bichlorid, but the thorough irrigation of the anterior urethra by means of a small straight glass tube fused at the end, care being taken not to allow the irrigating fluid to wash back of the external sphincter urethral material containing possibly smegma bacilli. This is accomplished by not elevating the irrigating tank too high and thereby causing too much pressure. Having accomplished this, the patient is instructed to empty his full bladder in three clean sterile glasses. A specimen from the third glass is centrifugalized in a high powered centrifuge, care being taken that only clean and sterile tubes and pipettes are used for the purpose. Having done all this, an acid fast, red staining bacillus found in a smear stained by any of the usual technics for identifying the Koch bacillus, can be regarded as the tubercle bacillus. If this technic is followed, the bacillus will be demonstrable in the vast majority of cases. Negative findings, however, do not exclude renal tuberculosis any more than the failure to find the tubercle bacillus in the sputum excludes pulmonary tuberculosis. In case of failure to demonstrate the bacillus, resort must be made to the inoculation test.

ANIMAL INOCULATION.—A more accurate method, though more troublesome and more time-consuming, is the inoculation test. It is made when tuberculosis is suspected and the urine examination is negative to tubercle bacilli. Indeed, some authorities maintain that this test should be carried out in all cases, not only when the urine examination is negative for the tubercle bacilli, but as a control in the cases where an acid-fast bacillus has been demonstrated. The technic for inoculating a guinea pig for tuberculosis will be found in any standard textbook on pathology. Briefly, it is as follows: A 2 c.c. syringe full of urine, obtained after the precautions cited above, are injected under the skin of the pig's abdomen. At the end of five weeks, earlier if signs are already apparent, the pig is killed and autopsied. Smears from the internal organs and lymph glands, particularly in the one near the site of the injection are made and studied for the tubercle bacillus. Knowing the extreme susceptibility of the guinea pig for tuberculosis, it goes without saying that the ones selected must not only be healthy or vigorous looking, but during the incubation period must be placed under the most favorable hygienic surroundings and protected from accidental tuberculous infection. This test, while most valuable, is not often relied upon, not only because it is troublesome, but because it is too time-consuming. It, too, might fail, as in the case of urine obtained from a patient,—the subject of an autonephrectomy or where there is a temporary blocking of the tubercle bacillus. However, this is a rare occurrence.

CULTURAL METHODS.—Brown and Petroeff have suggested a method of differentiating the smegma and tubercle bacilli based on the easy cultivation of the tubercle bacilli and the impossibility of cultivating the smegma bacilli.

X-RAY DIAGNOSIS.—The tuberculous cavities often become filled with inspissated cheesy-masses covered with phosphatic incrustations. X-ray in these cases will show dense shadows, and may be mistaken for stone. Waters and Colston have called special attention to this and have shown the method of differentiating x-ray shadows due to tuberculosis and those due to stone. This method of diagnosis may at times be quite helpful, especially in advanced tuberculosis of the bladder, secondary to kidney tuberculosis. Owing to a vesical irritability and the extreme cystitis, cystoscopy and ureter catheterization are impossible. There may be no kidney signs or symptoms suggesting which kidney is involved. If an x-ray of each kidney were taken and one were negative and the other showed extensive shadows in the other kidney, one would be justified in diagnosing advanced tuberculosis of that kidney and subjecting the patient to operative interference.

CYSTOSCOPY AND URETER CATHETERIZATION.—By far the most important adjuncts in the diagnosis of renal tuberculosis are cystoscopy and ureter catheterization. By cystoscopy one can often not only diagnose cystitis of tubercular origin, but obtain valuable information by the study of the ureter orifice, which will show on which side the renal tuberculosis is present. There is nothing pathognomonic about the cystoscopic picture of the bladder in tuberculosis unless one sees discrete miliary tubercles, which appear as small, grayish elevations, surrounded by a zone of hyperemia. These tubercles soon break down and appear then as small irregular shallow ulcers. These tubercles and ulcerations appear usually around the mouth of the ureter on the side the tuberculosis exists. So constant is this finding, that one is justified in making a diagnosis of tuberculosis of the kidney on the side that they are observed. Various changes may take place in the ureter mouth itself, *e. g.*, golf-holed appearance from ulceration in the ureter mouth itself, and rigidity of the ureter walls from tuberculous infiltration therein, preventing its entire closure and sluggish action. Again the ureter mouth may show retraction, caused by the thickening and shortening of the ureter, resulting in distention and displacement of the ureter mouth from its normal position, making it difficult or impossible to locate.

URETER CATHETERIZATION.—By ureter catheterization, we obtain the most valuable information, not only leading us very often to the diagnosis, but the prognosis and the line of treatment necessary. In studying any kidney condition, not only is it necessary to diagnose the presence of a diseased condition, *e. g.*, renal tuberculosis, but other associated factors or information may be just as necessary. One must learn, for example, if the patient has two kidneys. It is estimated that about one in every 2,500 individuals has congenital absence of one kidney. One such case has already been cited. Secondly, we must determine whether the patient has what is called an infantile or congenitally atrophic kidney, which is not very uncommon; and thirdly, we must learn whether the infection is unilateral or bilateral. Upon this information will the question of operation and character of treatment be determined. All this is accomplished by ureter catheterization. Through this agency, one obtains the urine separately from each kidney, and is thereby enabled to subject it to a careful microscopical, bacteriological and chemical examination. Further, by means of functional tests we can determine the amount of damage done to the diseased kidney and the normalcy of its fellow. Of the various functional tests, by far the most simple and practical is the phenolsulphonephthaleïn test of Geraghty and Rowntree. Chromocystoscopy, popularized in this country by Thomas, is valuable at times in these cases, where the ureter cannot be located owing to physical conditions present. This test consists of injecting intravenously a solution of indigocarmin and watching the efflux from the ureter mouths. This test has also been recommended as a functional test on the assumption that ureter catheterization ought not to be carried out in suspected cases of renal tuberculosis for fear that the catheter going up a normal kidney may carry along with it tuberculous urine and infect it. The author has never seen this occur and does not believe in it.

TUBERCULIN TEST.—Two principal methods are employed, the Koch's subcutaneous method, and the Von Pirquet's scarification method. In each, Koch's old tuberculin (O.T.) is used. The latter is a filtrate of a concentrated bouillon culture of tubercle bacilli, containing, therefore, the toxin of the bacteria. The one generally employed is Koch's subcutaneous method and the test is of value not only because it produces a general reaction which would merely indicate tuberculosis somewhere in the body, but also causes a focal reaction. The latter is characterized by an increase in the intensity of the symptoms complained of. For example, if a patient suffering with a pyuria, hematuria, frequency, urgency and tenderness in the region of the bladder or the kidney has these symptoms aggravated following a tuberculin injection, it would be safe to say that the pathological lesion in the genito-urinary tract causing them was tuberculous. Before applying the tuberculin test, certain preliminaries must be carried out. The temperature chart is observed for several days to determine its usual variations. The test is not applicable in all cases. Contra-indications to the test are a markedly febrile course, general miliary tuberculosis, acute or advanced tuberculosis, tuberculous meningitis, the terminal stages of other diseases, and during convalescence from acute febrile diseases. The usual dose is 0.5 milligram (.0077 grain). A positive reaction consists in an elevation of at least one degree Fahrenheit, focal reaction and a local reaction at the site of the injection. If no reaction of any kind is produced, the injection may be repeated, increasing the dosage gradually every 3 to 5 days until as much as 5 mg. are given. The Von Pirquet test is very seldom employed, because it produces only a local reaction, which merely determines the presence of a tuberculous focus somewhere in the body.

GENERAL PHYSICAL EXAMINATION AND HISTORY.—In the diagnosis a careful history and physical examination may reveal considerable confirmatory evidence and should always be carried out. A family history of tuberculosis or a history of exposure to the disease in a person suffering with urinary symptoms, may lead one to suspect tuberculosis of the urinary tract. The absence of such a history, however, has no special significance. The personal history and examination of the patient are more important. Careful inquiry and examination should be made into the past history of the patient, particularly regarding a preexisting pleurisy, pneumonia, influenza, cough, night sweats, feverishness, bone sinuses, joint trouble or glandular swellings. A careful physical and x-ray examination of the lungs should be made, preferably by an expert, to determine an active or healed focus in the lungs.

DIAGNOSIS BY OPERATION.—The value of this method of diagnosis is held by most authorities, and, of course, is recommended only when other methods are not applicable or fail to achieve the desired result. Formerly it was the practice to expose the kidney itself and by palpation and visual examination determine the diagnosis. Lately the technic has been improved by an extraperitoneal exposure and palpation of the ureter at the pelvic brim and preferably by making a loin incision and doing a nephrectomy at the same time, should the ureter exhibit the pipestem-like induration that is characteristic of renal tuberculosis above. The method of diagnosis by operation is unreliable and misleading.

Course and Prognosis.—It is held by most authorities that spontaneous cure of a tuberculous kidney never takes place. While it must be admitted that this is true in the vast majority of cases the author has had personal experience which convinces to the contrary. For example, he saw in consultation several years ago with a surgical colleague, a physician in whom after a thorough study, he made the diagnosis of bilateral kidney tuberculosis and advised against operation. The surgeon, because the x-ray showed dense shadows in one kidney (due to calcareous caseous foci), diagnosed renal calculi and decided to operate and removed the kidney, which was tubercular. Several years later the remaining kidney which formerly had been excreting urine containing much pus and blood had shown considerable reduction in phenolsulphonephthalein function, was now excreting perfectly clear urine and the kidney function was not only normal for one kidney but normal for two kidneys, showing it had undergone compensatory hypertrophy. The perfectly clear urine also indicated a healed process in the only kidney. However, as stated, this is extremely rare. Tubercular kidneys tend to gradually grow worse and, unless modified by surgical intervention, sooner or later involve the other kidney and the patient dies from renal insufficiency, or a general disseminated tuberculosis. This progress may be very rapid or may be prolonged for many years, but death usually occurs in from five to ten years. As has been stated above marked remissions in the symptoms may occur and lull the patient and physician into a false sense of security. This latter occurrence may be due to autonephrectomy (*q. v.*). If patients are operated upon by urologists who make use of all the preliminary methods of diagnosis now at their command, the immediate mortality rate will not be over 3 per cent. The later mortality rate will be between 10 and 20 per cent. Several factors influence the prognosis in the operative cases, *e. g.,* tuberculous lesions elsewhere in the body, the physical condition of the individual at the time of operation, his resistance, etc. The author has operated upon a number of young patients with early renal tuberculosis of slight grade and in whom the physical condition seemed good and the rest of the body obviously normal. Yet, following nephrectomy, they develped lesions elsewhere in the body, *e. g.,* of the intestines, and succumbed rapidly. Older patients do not seem to behave in this fashion. This brings up the questions of artificial immunization by tuberculin, and hygienic and dietetic treatment in these cases before resorting to operative intervention. More statistics and data will have to be made available before this question can be properly settled. At the present time the treatment deemed best is immediate nephrectomy.

Treatment.—When there are no contra-indications, the only treatment to be considered as offering any great hope of success is **nephrectomy,** no matter how small the lesion in the kidney may be. At times, however, this will not be possible on account of various contra-indications.

CONTRA-INDICATIONS.—*Other Tuberculous Lesions in the Body.*—Ordinarily speaking a patient with extensive lesions in the lungs, joints, bones, genitals, or peritoneum is not to be nephrectomized for renal tuberculosis. To operate in the presence of these conditions, tends either to invite death from a general miliary infection or aggravation of the remaining lesions. The author has had exceptions to this rule, however. For example, a patient with a tuberculous condition of the lungs, left kidney, bladder, prostate, seminal vesicles, and both epididymes, showed remarkable improvement following the removal of the diseased kidney and one fistulous tuberculous epididymis. His urinary symptoms cleared up, and the tuberculous condition in the prostate, seminal vesicles, and remaining epididymis could not be elicited by palpation at an examination made one year later. The author has reported this case along with a number of others and the explanation offered was that the removal of the tuberculous foci permitted the remaining anti-bodies to more than cope with the now reduced tuberculous toxins. Quite recently as a palliative measure, the author removed under spinal anesthesia without the least shock or difficulty an advanced right tuberculous kidney, which was beginning to cause bladder symptoms, in a patient with advanced pulmonary tuberculosis. From what has been said, therefore, judgment must be exercised in the proper handling of this type of case.

Operation in Bilateral Cases.—If the tuberculous condition involves both kidneys and the lesions in both are advanced or moderately advanced, operation is contra-indicated. However, if the condition is advanced in the one kidney and the lesions in the other kidney are slight, nephrectomy of the more diseased kidney ought to be carried out. The remaining kidney then may be treated by tuberculin, or by hygienic, dietetic and climatic measures in the hope of staying its process. It may or may not check the process in the remaining kidney and prolong life.

General Hygienic and Constitutional Treatment.—If for some reason or other, nephrectomy cannot be carried out, or is inadvisable or if the same has been carried out, certain general measures remain to be considered. These are tuberculin, hygiene, climate, diet, and drugs.

Tuberculin.—Every patient who has been operated upon for renal tuberculosis or in whom operation is contra-indicated should receive **tuberculin treatment.** In the former, it will tend to strengthen him against recurrences or the development of new lesions or the lighting up of old ones by raising his immunity. It does not always succeed and is not the most important factor. At most it is only an adjunct. Various forms of tuberculin are used. The initial dose is from 0.0001 to 0.001 milligram. These doses are doubled at intervals of from three to five days or longer until the patient is receiving 50 to 100 milligrams at a dose. The dosage and frequency of administration is gauged by clinical signs of reaction, local, focal and constitutional. Too much reaction is to be avoided and, as a rule, we attempt to carry these patients up to a considerable dosage without producing much discomfort. If the latter should occur, the treatment must be entirely suspended until two or three weeks after all symptoms have subsided, when it is recommenced at a dosage of one-thousandth or one-hundredth of that which caused the disturbance. This treatment should be kept up for a period of many months and, while the patient is receiving this, careful notation is made of the progress he is making by recording the weight, pulse, and temperature. The patient's lungs are examined from time to time, and the condition or progress of other organs determined.

The patient ought to be confided in and the reason for all measures taken explained to him, so that one will not only elicit his interest but secure his better coöperation.

Hygienic, Dietetic and Climatic Treatment.—A patient with renal tuberculosis should receive the same hygienic, climatic, and dietetic treatment given to **pulmonary phthisis.**

Drugs.—There is no special drug therapy to be recommended for persons suffering with renal tuberculosis. If the patients have considerable frequency and painful micturition, the administration of **sandalwood oil capsules** (minims x-xx [.6 to 1.25 c.c.] t.i.d.) may be helpful. **Hexamethylen** and its compounds are to be **avoided**, as they do no good in reducing the infection and owing to their irritating qualities may aggravate the symptoms. Local treatment will be more discussed under the heading of bladder tuberculosis. If the patient, however, has a tubercular stricture secondary to a renal lesion, considerable improvement in the colicky symptoms and the kidney itself may be noted following **ureter dilatation,** *e. g.*, the case cited above of the patient with very severe renal pains simulating kidney colic, was not only fully relieved of his recurrent attacks of colic by ureter dilation, but considerable improvement in the kidney was noted by the clearer appearance of the urine and its function and by the gain in weight and general well-being of the patient. This patient's ureter is now dilated about once in every three or four months. He not only eats and sleeps well, maintains his weight and strength, but continues his daily office work in a crowded city. **Pelvic lavage** with silver nitrate and other antiseptics is not only valueless but **harmful.**

PREGNANCY IN RENAL TUBERCULOSIS.—As a general rule, patients suffering with renal tuberculosis should **avoid pregnancy**, as the extra strain put upon the kidneys may result in disaster. Patients who have been nephrectomized for tuberculosis should wait at least two years before becoming pregnant, providing the remaining kidney has a good function and there is no contra-indication as far as other organs are concerned. Experience has taught us that many patients who have been nephrectomized for tuberculosis have subsequently gone through a normal pregnancy without the least damage to the remaining kidney

Pathology.—ACUTE TUBERCULOSIS.—Acute tuberculosis of the kidney has small practical interest, because it is only a part of a general miliary process which overshadows it. It is always bilateral, rapidly progressive and fatal. The kidneys when examined postmortem, are enlarged, purplish in color and studded throughout with innumerable

CHRONIC TUBERCULOSIS.—Keyes divides chronic tuberculosis into three types: Parenchymatous, papillary, and pelvic. This condition is occasionally referred to as *surgical tuberculosis of the kidney,* because it is amenable to treatment and cure by surgical intervention. The lesions may begin and are most prominent either in the parenchymatous, papillary or pelvic portions of the kidney. The extent of the pathological process in the kidney when seen, varies from the one extreme of a normal looking kidney studded with an occasional minute abscess, to the most destructive process involving the entire organ. In the parenchymatous type, the initial lesion begins in the renal parenchyma and practically always at either the upper or lower kidney pole. Subsequently, the central portion may become involved. The lesions begin first as one or more small whitish discrete-like areas, which soon coalesce and undergo necrosis and caseation forming at first hand nodules and subsequently cheesy cavities containing flaky pus and a shaggy surface. The cheesy cavities or foci of tuberculous deposit are surrounded by zones of inflammatory exudation and a more or less generalized interstitial nephritis. The tuberculous process progresses by direct continuity of tissue, or new areas of foci of tuberculous deposit form. After a time, which varies in the individual case, the abscesses containing the tubercle bacilli ulcerate or break, permitting their spread back into the kidney tissue or outwards into the kidney pelvis. This direct discharge of bacilli or tuberculous laden urine may now infect the pelvis, various portions of the ureter, bladder, etc.

PAPILLARY TUBERCULOSIS.—In this type, which is extremely rare, the tuberculous process begins in one of the renal papillæ, ulcerates through it and then involves the pelvis. The author once operated on such a case. At the time of operation the kidney looked perfectly normal; even bisection of the organ failed to reveal the lesion. It was feared for a while that an erroneous diagnosis had been made. However, when the kidney was further studied in the laboratory, a papillary tuberculosis, confined to one papilla, with an extensive pelvic lesion was found. The pelvic mucosa in these cases has lost its sheen, and its surface may be dotted with numerous discrete and confluent tubercles. Ulcerations may be present, accompanied by an infiltration and thickening of the pelvic walls and showing no tendency to perforation. As a result of these changes, the cavity of the pelvis may be considerably encroached upon, causing renal retention and dilation, the latter leading to a tuberculous pyonephrosis.

TUBERCULOUS PYONEPHROSIS.—Tuberculous pyonephrosis is caused by the development of some obstructive condition in the pelvis or ureter causing renal distention and dilatation or it may be caused by the confluence of tuberculous nodules forming abscess cavities. The obstructive influence usually found is a tuberculous stricture of the ureter. Pelvic retention may occur in tuberculosis of the kidney, even though no stricture is demonstrable. It is probable that as a result of the disease, a loss of muscular tone supervenes sufficient to lead to renal retention. In these cases the kidney is considerably increased in size, is lobulated and rounded in contour. The cortex is considerably thinner, the whole appearing more like a partitioned or non-partitioned membranous sac than kidney tissue. The calyces, if present, will be dilated and tubercles may be noted here and there. The interior of the kidney will be filled with a thin, flaky, thick, non-odorous, cheesy-like pus.

AUTO-NEPHRECTOMY.—In this interesting condition the kidney has gone on to complete destruction and is completely functionless and walled off from the rest of the body. Not only is no urine secreted, but even the circulation in the renal artery and vein has become obliterated by thrombosis. While manipulating these kidneys at operation, the pedicle is so atrophied and friable that it occasionally becomes detached from the surrounding tissues without resultant bleeding or danger. In these cases, the contents of the caseous cavities often become inspissated, producing a thick, soft, white, putty-like mass, or the latter may become impregnated with calcium salts. Such kidneys will give a dense shadow when x-rayed and are often erroneously diagnosed as renal calculus. Tubercle bacilli may nevertheless be found in these kidneys, and it is even possible for them to act as foci from which other organs may become involved and from which a miliary process results.

Secondary Sclerotic Changes.—The fatty capsule surrounding the kidney undergoes chronic inflammation and becomes converted into fibrous tissue. The latter in some instances becomes most extensive. This causes marked adhesions between the kidney and perirenal tissues and is of practical importance to the surgeon who would find nephrectomy difficult unless he used the so-called intracapsular method.

Secondary Pyogenic Changes.—Mixed infection with other organisms, especially of the colon variety often supervenes shortly after a tubercular focus ruptures into the pelvis. It usually escapes notice as it gives rise to no special complications or symptomatology. It does not, as a rule, cause acute suppuration within the kidney even in the pyonephrotic cases. Occasionally, however, extension of the pyogenic process through the true capsule of the kidney into the tissues of the perirenal envelope takes place resulting in the formation of an acute suppurative perinephritis (perinephritic abscess). This complication usually occurs in the pyonephrotic stage where there is a mixed infection of the tubercle bacillus and pyogenic organisms.

Toxic Tuberculous Nephritis.—As a result of the toxins elaborated by the tuberculous kidney, the other kidney becomes the seat of a "medical" or toxic nephritis or albuminuria. In most cases, the urine shows a definite ring of albumin without either pathological elements, such as casts, pus or blood cells. This is a purely functional derangement and it disappears promptly following removal of the tuberculous kidney. Occasionally, there is a group of cases encountered, where casts are present and epithelial desquamation of the renal tubules takes place, and a still rarer group where a true toxic parenchymatous nephritis exists. The practical importance of recognizing the above conditions supervenes, when deciding on the prognosis of the patient, or determining if a nephrectomy of the tuberculous kidney should be carried out.

TUBERCULOSIS OF THE BLADDER

Etiology.—Tuberculosis of the bladder is practically always secondary to renal or genital tuberculosis, usually the former. Primary tuberculosis of the bladder can, however, take place. Such cases have been reported by Casper, Fenwick and Kelly, Saxtorph, Heiberg, etc. These cases have frequently followed gonorrhea, which is supposed to predispose to tuberculosis. As has been already mentioned (*see* Renal Tu-

BERCULOSIS) tubercle bacilli may filter through the kidneys without producing any demonstrable lesions therein and descending may find the bladder a favorable soil for their reception, owing to its lessened resistance from various causes. Pure tubercular cystitis may be seen, but usually secondary infection is present, the complicating organisms most often being the colon bacillus.

AGE.—Like tuberculosis of the kidneys, it is a disease of young life, occurring between the ages of twenty and forty. It has been observed, however, in very young children and in the senile.

SEX.—Males are affected about twice as often as females. The explanation for this greater frequency lies in the greater length and complication of the male urethra, and to the fact that vesical tuberculosis is often secondary to genital tuberculosis in the male, while in the female this occurrence practically never happens.

EXCITING CAUSE.—The exciting cause is the tubercle bacillus.

PREDISPOSING CAUSES.—The predisposing causes are traumatism and obstruction, although more often than not no such history will be obtainable. It is very doubtful if gonorrhea predisposes to the development of vesical tuberculosis. The most important predisposing factor is the presence of the disease elsewhere in the body and the tubercular tendency. Practically every case of renal tuberculosis discharges tuberculous laden urine into the bladder, and in from 4 to 10 per cent. of genital tuberculosis cases the presence of tubercle bacilli in the urine will be revealed. Tubercle bacilli may be found in the urine of pulmonary phthisis and other forms of systemic tuberculosis far distant from the urinary tract. As has already been stated, vesical tuberculosis is most commonly secondary to renal tuberculosis, but it often happens when the case is first seen that so many organs of the genito-urinary tract are coincidentally involved in the process, that it is impossible to say whether it is secondary to the renal tuberculosis, or secondary to similar diseases in the prostate, seminal vesicles, or epididymis.

METHOD OF INVASION.—This is most commonly by direct extension from the kidney above or the genital below. It may also become involved by hematogenous or lymphatic extension and possibly through sexual intercourse.

Symptomatology.—There is nothing pathognomonic about the cystitis caused by the tubercle bacillus. However, certain features about it are very suggestive as it becomes advanced. The only certain means of diagnosis is the demonstration of the tubercle bacillus in the urine and the cystoscopic findings. The disease may be very slow in its onset, and does not necessarily follow quickly upon the heels of the renal infection. Indeed, tuberculosis of the kidney may exist a long time before the bladder becomes involved. The disease is usually insidious in its onset, progresses slowly, and like tuberculosis in other parts of the body, exhibits periods or remissions and exacerbations. The first symptom the patient usually notices is vesical irritability, followed very shortly by hematuria. The vesical irritability giving rise to frequency, is nocturnal as well as diurnal, and is not very much influenced by rest or especially aggravated by exercise, diet, etc. As the disease progresses, the frequency increases until the patient is compelled to pass his urine every few minutes. This may be so marked that it often amounts to incontinence. The latter may be a symptom, especially at night. Enuresis and incontinence may be noted in children suffering from bladder tuberculosis. After this symptom has existed for a short while, pain develops. At first it is slight and noticed at the end of urination. It may be felt in the suprapubic region, the perineum, the under surface of the penis, at the glans penis or it may radiate to the region of the testicles. After a time owing to the spasm which the pain occasions, these symptoms are aggravated and the patients suffer most intensely. When ulceration takes place or secondary infection supervenes this pain is not only intensified but it is felt just before and during, as well as at the end of urination. This pain is associated with an uncontrollable spasm, resulting in the involuntary passage of urine down the patient's thigh, etc. This miserable condition of the patient is not much alleviated by the onset of night or rest in bed. Instrumentation is very badly tolerated, and irrigations with various antiseptics, especially silver nitrate, aggravate the symptoms and points of diagnostic importance. The presence of calculous material in the urine is often noted. Hematuria is another symptom and is as common as the frequency and pain in the bladder tuberculosis. It comes on with or shortly after the onset of the above symptoms and persists throughout to the end. In the early stages it is apt to be terminal in nature but it may be mixed, producing a smoky urine. The terminal hematuria is due to the final muscular contraction of the bladder expelling the last few drops of urine. It is especially seen in those cases where the infection travels upward from the genital tract and the most marked changes are at the vesical neck. The hematuria is not constant, suffers remissions and exacerbations. It finally loses its terminal characteristic and is seen admixed with all the urine giving it a smoky hue. During the period of remissions, even though the urine looks clear, the microscope will invariably demonstrate red blood-cells and albumin will be present. The bleeding is seldom associated with large clots, and retention from clots rarely takes place. Instrumentation aggravates the hematuria, but exercise, diet and rest do not seem to influence it one way or the other. It is seen by night as well as by day. It is differentiated from the hematuria of bladder stone, which is aggravated by jolting or exercise, and from the hematuria of vesical neoplasm by its lack of great profuseness and the rarity of retention from clot formation.

THE URINE.—There is one great characteristic feature of the urine in tubercular cystitis, and that is its acidity. Even when mixed infection with the ammoniogenic cocci is present, it is rare to see the urine alkaline. Its specific gravity is low. It is always bloody, the latter varying with its demonstration only on microscopic examination, or it may be of a smoky hue or even bright red. It often presents a pale, milky appearance. Albumin is always in evidence. Microscopically, in addition to the blood, pus cells in great numbers and epithelial cells are present. Bacteria may be absent until secondary or mixed infection supervenes. The complicating organisms are usually the colon bacilli and the staphylococci. It is well to repeat what has been said regarding the urine in renal tuberculosis. Pus in the urine without organisms, by the ordinary staining methods, generally means tuberculosis or gonorrhea. The special staining methods for tubercle bacilli in the urine will reveal their presence in about 80 per cent. of the cases if the search made is thorough and careful.

Diagnosis.—Any cystitis appearing in a young person without a history of previous disease of the lower genito-urinary tract, such as gonorrhea, or of prostatic disease, etc., should cause one to suspect bladder tuberculosis. This suspicion is strengthened, if instrumentation or irrigations, particularly of silver nitrate, aggravate it. The certain diagnosis, however, is made by finding the tubercule bacillus in the urine, or by a positive inoculation test and by the cystoscopic findings.

CYSTOSCOPIC FINDINGS.—The cystoscopic findings in vesical tuberculosis are rather characteristic. They are as follows:

(*a*) Bladder contracted and irritable. It may be so contracted that it will hold only one or two ounces of fluid and so irritable that general anesthesia is often necessary in order to carry out the cystoscopic examination.

(*b*) Hyperemia, edema or ulceration around either ureteral orifice if the lesion is secondary to the kidney, and the same findings predominating about the vesical orifice if the disease is secondary to a primary focus in the prostate, seminal vesicles, or epididymis. These changes have been discussed more in detail in discussing renal tuberculosis. As the disease progresses the cystitis may become general, and one will see ulcers, vegetations, villous outgrowths, phosphatic incrustations, etc.

GENERAL EXAMINATION.—As in renal tuberculosis, a general physical examination is important. The symptoms, history, presence of tuberculosis in the genital tract, lungs, bone, glands, etc., should be sought after, as has been discussed more fully in renal tuberculosis.

Treatment.—From what has been said, the most important element in the treatment of vesical tuberculosis is the **removal,** if possible, of the **primary focus.** If the disease, however, is secondary to a bilateral renal infection or an extensive genital tuberculosis, this might not be practicable. Resort must then be had to both **general** and **local forms** of treatment.

GENERAL TREATMENT.—This consists exactly of the same measures discussed under the head of renal tuberculosis, *viz.*, **hygienic, dietetic, climatic, and tuberculin treatment. Tonics,** such as **iron, cod-liver oil, guaiacol, creosote** and other measures recommended for other forms of tuberculosis may be tried. **Sandalwood oil capsules** (minims x to xx [.6 to 1.25 c.c.] t. i. d.) until renal irritation is produced or the administration of **alkalies** may soothe the inflamed and irritable bladder. Urinary antiseptics, especially **urotropin** and its equivalents do **more harm than good** on account of their irritating qualities.

LOCAL TREATMENT.—Bladder irritations are very poorly tolerated and aggravate rather than ameliorate the symptoms. The best local measures are instillations of **carbolic acid,** 1-200 to 1-50, as first recommended by Rovsing. Keyes speaks highly of daily instillations of **bichlorid of mercury.** He recommends from 2 to 10 minims of a

1/25,000 solution and an increase of the strength of the latter as rapidly as the patient's symptoms permit. **Iodoform** as an emulsion, 10 per cent., is lauded by some. Some claim **gomenol** better than anything yet recommended. High frequency applications to the ulcers, injections of sterile air, nascent iodin, etc., all have their advocates. The treatment of tuberculosis of the bladder by local treatment will usually be found discouraging, no matter what form or method is used.

OPERATIVE TREATMENT.—This is practically never considered, unless the symptoms are most agonizing and unbearable when a **suprapubic drainage** is carried out. This almost invariably leaves the patient with an intractable fistula and may add to the patient's discomfort and troubles. Some surgeons have operated in extreme cases, after explaining the hazards and the miserable probable future prospects of the patient. The operations performed have been the extirpation of the whole mucous membrane, excision of the ulcers, curretting, cauterizing and burning the ulcerations through a suprapubic or perineal wound. Medication through a suprapubic wound may ameliorate the symptoms. The drugs used are the ones discussed under the heading of local treatment.

Prognosis.—The course is slow and tends to become gradually worse unless the primary focus is removed. If the condition is recognized fairly early and is secondary to a unilateral renal tuberculosis, removal of the offending kidney will stop the further descent of tubercle bacilli to the bladder, with the result of a spontaneous healing of the bladder lesions. The disease may remain more or less stationary for many years. It not only makes life miserable by the intensity of its symptoms, but death, when it occurs, is due to pulmonary or renal involvement or the development of a terminal, miliary tuberculosis.

Pathology.—The picture of vesical tuberculosis may show great diversity. It may occur as a simple vesical tuberculosis or as a tuberculous cystitis. The initial lesions usually begin about either ureter orifice if the disease is secondary to the kidney, and about the vesical orifice or trigone if the disease results as an upward extension from the genital tract. At times during a cystoscopy, we can by observing the ureteral orifices or the vesical neck learn whether the primary cause of the infection was in either kidney or in the genital tract. However, it often happens that owing to mixed infection there will be present a more or less generalized cystitis, making it impossible to locate the primary source of the disease. Tubercles in beginning vesical tuberculosis appear as minute whitish areas, the size of a pinhead, surrounded by a zone of hyperemia. They are occasionally disseminated, but more often confluent over the bladder wall and in irregular areas, while the intervening vesical mucous membrane is red, puffy and edematous. When this is marked and extensive, the mucous membrane appears velvety and smooth, because the tubercular deposits occur in the subepithelial tissues. After a while, these small areas change their color from a grayish to a yellowish hue, owing to caseation. At this stage, the epithelium degenerates, leaving a superficial ulceration. The tubercular ulcers are usually rounded and even if confluent the line of demarcation soon disappears. The floor of the ulcer is shaggy and of a grayish yellow color.

The edges are often undermined, and the whole ulcer is surrounded by an intense zone of congestion. In some cases the ulceration may extend to the muscular coat. This is extremely rare, however. Still rarer are extensions sufficiently deep to cause perforations resulting in perivesical abscesses, or fistulæ opening into the rectum, vagina or hypogastrium. In some of the advanced cases, owing to extensive destruction of the mucous membrane and submucosa, inflammatory infiltration of the muscular walls with subsequent contracture takes place, producing the typical tubercular bladder, *viz.*, thick, rigid, non-dilatable walls, causing a marked diminution in its interior capacity (contracted bladder). In well-marked cases there is in addition a pericystitis, which consists of a fibrolipomatous sclerosis, resulting in adhesions between the bladder and adjacent structures. Examination will frequently show, even in the cases secondary to renal involvement, extension to the posterior urethra. Extension to the anterior urethra, however, is extremely rare. The author has seen it in only one case, following a meatotomy. This histological picture shows the characteristic features of tubercle formation similar to that found elsewhere.

TUBERCULOSIS OF THE EPIDIDYMIS, TESTICLE, SEMINAL VESICLES, PROSTATE, URETHRA AND PENIS

(Genital Tuberculosis)

Introduction.—It is advisable in discussing tuberculosis of the epididymis, testicle, prostate, seminal vesicles, urethra and penis to consider them jointly under the heading of genital tuberculosis.

Etiology.—The disease begins in the epididymis and then travels by means of the lymphatic system to the seminal vesicles and prostate. The testicles and bladder may also be involved. When these structures become involved, it is usually by direct continuity of tissue or through the lymphatics. There is a great tendency of the disease beginning in the epididymis to attack its opposite fellow. This occurs in about 50 per cent. of the cases.

A few authorities maintain that the disease starts in the seminal vesicles and then extends to the prostate and epididymis. The weight of evidence, however, favors the epididymis as the primary source of the tuberculosis in the genital tract. The infection beginning in the epididymis is supposed to be through the hematogenous route, and this accounts for the disease when it is primary in the epididymis beginning often in the globus major. A number of authorities, however, claim that it is more often primary in the globus minor. In the vast majority of cases of epididymal tuberculosis, coincident involvement of the prostate and seminal vesicles exist. Thus Barney, in a study of 1,862 cases of genito-urinary tuberculosis, found the epididymis tuberculous in 617 out of 821 cases in which the condition of the epididymis was described, or 75.1 per cent. The prostate and seminal vesicles together were said to have shown tuberculosis in 1,169 out of 1,675 cases, or

69.7 per cent., while disease in the testicle was noted in 57.6 per cent., or 739 cases. Primary tuberculosis of the penis, testicle, and urethra are extremely rare. Like in renal tuberculosis, genital tuberculosis is usually secondary to tuberculosis elsewhere in the body, although it too may be primary as far as the whole body is concerned. In Barney's own series of 154 cases of tuberculosis of the epididymis, tuberculosis of other organs was found in 55.8 per cent. It is most often secondary to lung tuberculosis. The percentage of lung tuberculosis preceding genital tuberculosis ranges between 22.7 per cent. (Barney), up to 81 per cent. (Oppenheim), or even higher (Steinthal). This is important to remember in selecting the anesthetic for operative intervention. Next in point of frequency is the kidney and then bone infection.

ACTIVE CAUSE.—The tubercle bacillus is the active cause.

PREDISPOSING CAUSES.—Although the tubercle bacillus is the active cause of genital tuberculosis, certain predisposing causes are essential before the bacilli can gain a foothold. The epididymis, testicle, seminal vesicles and prostate can, like the kidney, assume an excretory rôle and eliminate organisms of various kinds without any harm or pathological changes being produced. The predisposing causes are the tubercular diathesis; a pre-existing tuberculosis elsewhere in the body; and lessened resistance on account of trauma, gonorrhea or syphilis.

There is some discussion in the literature regarding the possibility of infection occurring during coitus. Frank and Kraemer regard tuberculosis occurring from coitus as impossible. On the other hand Senn, Oberndorfer and Williams believe in this mode of transmission. Tubercle bacilli have been found in the healthy epididymis. Palladino-Blandini in 1900, Delli Sante in 1903, and others have shown that all bacteria, including the tubercle bacilli, when injected into the urethra near the meatus may reach the epididymis, but under such circumstances cause no disturbance. Before infection can take place, obstruction or trauma must also be present. These facts tend to prove that infection during coitus must be admitted as possible but not probable, as it would be difficult to expect clinically a combination of these two essentials at the same time, *viz.*, intromission of a large number of tubercle bacilli into the urethra and a traumatized testicle and epididymis. Pinaud cites 4 cases of tuberculosis of the penis from fellatio. A number of cases have followed circumcision done by the old Jewish ritual. The question of potency and sterility is often inquired into. The testicle may be the seat of an extensive tuberculous process and spermatozoa, nevertheless, may be present in large numbers. Similarly, the sexual desire remains unimpaired. Even if both testicles are removed by operative intervention, the patient may still get erections and have intercourse, providing the castration occurs in adult life.

Age.—About 60 per cent. of the cases occur between the age of 20 and 40. It has been found in the infant and the aged beyond the eightieth year.

TUBERCULOSIS OF THE PROSTATE

Pathogenesis.—Tuberculosis of the prostate has been studied rather extensively, both clinically and experimentally, to determine its pathogenesis. George Walker's classical study shows that the initial process begins just under the epithelial layer of the ducts. Small tubercles form and they go through the process of tuberculization: caseation, abscess formation, and fistulization, or instead of the latter, it may end by cicatrization. Very rarely, if ever, it may terminate by calcification. Grossly the lesion may reveal nothing by rectal touch. Usually, however, the prostate is slightly increased in size, irregular in outline, and in both lobes firm and nodular to the touch. If abscess formation takes place fluctuation will be detected. When an abscess forms and ruptures it is almost invariably into the urethra. Rarely it may rupture posteriorly into the rectum. When rupture into the urethra takes place, extension to the urethra and bladder follow. Invasion of the periprostatic tissues takes place, making removal of the organ difficult or impossible.

Symptoms and Diagnosis.—Prostatic tuberculosis may exist for many years without producing any symptoms. It is most often discovered while making a routine examination in a patient reporting for disease in the scrotal cavity. There is nothing characteristic about the symptomatology and feel of the tuberculous prostate and the diagnosis is made only by finding evidence of tuberculous disease in the other organs of the genitourinary tract. Symptoms ascribed to prostatic tuberculosis, such as gleet, dysuria, hematuria, urethrorrhagia, etc., are due to extension of the disease to the urethra and bladder and are more properly symptoms of tuberculous disease in these structures. If the prostate abscesses, signs of fluctuation, pain and tenderness may be elicited on rectal palpation and justify the diagnosis of tuberculous abscess formation, if coincident tubercular disease in other organs exist.

Treatment.—The essential part of treatment is **removal**, if possible, of the **primary source of the infection**, which will be found to be most likely in the kidney or epididymis, usually the latter. There is a marked tendency for tuberculous disease in the prostate to undergo marked retrogression following removal of the infected epididymis. The rest of the treatment of prostatic tuberculosis is very much like that of vesical tuberculosis (*q. v.*).

Prognosis.—This is good until extension of the urethra and bladder takes place; after this occurs, the prognosis is the same as for vesical tuberculosis.

TUBERCULOSIS OF THE SEMINAL VESICLES

Owing to the proximity of the seminal vesicles to the prostate, tubercular disease in the vesicles, at least from a clinical or practical standpoint, is always associated with similar disease in the prostate. In the beginning, the disease affects only one vesicle; later both are involved.

Symptoms and Diagnosis.—What has been said about the symptomatology of prostatic tuberculosis applies with equal force to the similar infection in the seminal vesicles. The diagnosis of tuberculosis of the seminal vesicles, however, is a little more probable, if on rectal examination one feels in the vesicle typical, hard, nodulated areas. More often, though, we will feel a simple induration of the vesicle, that will not serve to distinguish it from other forms of chronic vesicular inflammation. The vesicle in tuberculosis is usually tender on palpation and its contents often contain the tubercle bacilli. Massage of the vesicles, in some cases will initiate a similar infection in the epididymis, hence, the need of caution and gentleness in examination of these organs.

Treatment.—Massage and local treatment, from what has been said, predispose to epididymal infection, hence should be interdicted. The **hygienic, dietetic, climatic and tuberculin methods** of treatment outlined in vesical tuberculosis are of prime importance.

OPERATIVE TREATMENT.—Recently Young and a few others have been carrying out for tuberculosis of the seminal tract an extensive, radical dissection of those organs, the removal consisting of the epididymes, both vasæ, and both seminal vesicles, on the theory, that any tuberculous focus that is eradicable rids the patient of that much tuberculosis, with resulting increase of resistance to combat any remaining infection, etc. Most urologists do not follow this procedure, limiting the treatment to hygienic measures and carrying out vesiculectomy only in those cases where extensive caseation, suppuration, and fistulization exist.

Prognosis.—This is the same as in prostatic tuberculosis.

Pathology.—The same process of tuberculization occurs as in the prostate, *viz.*, caseation, abscess formation, cicatrizatioin, fistulization and calcification.

TUBERCULOSIS OF THE TESTICLE AND EPIDIDYMIS

Pathogenesis.—The organ primarly involved is the epididymis. From it the process extends to the testicle and vas. There are a few instances recorded where the testicle or tunica vaginalis became primarily involved, with secondary extension to the epididymis. The gross appearance of the testicle and epididymis in tuberculosis presents the following: The epididymis is enlarged, irregular and nodular, studded with miliary tubercles, or it may present areas of abscess formation and softening. Evidence of a more advanced process in the form of cicatrices, fistulæ or calcification may be noted. A point of diagnostic importance is the great tendency of the tuberculous epididymis to form abscesses and sinuses. These are usually found at the lower pole of the organ. There are very few scrotal diseases which cause fistulization, hence its occurrence is almost *prima facie* evidence of a tuberculous epididymis. The testicle may show areas of miliary abscesses, or caseous or necrotic foci may be noted. Occasionally the testicle may undergo a marked general fibrosis (orchitis fibrosa). The vas is often lumpy from tubercular deposits within its walls and its interior distended by products of inflammation. A perideferentitis may be present throughout its entire length. A thickened, nodular, enlarged vas is strong presumptive evidence of tuberculosis. The tunica vaginalis is practically always the seat of hydrocele and its walls may be studded with numerous tubercles. The microscopic picture of tuberculosis of the epididymis and testicle differs little from that seen affecting other organs or tissues.

Symptoms and Diagnosis.—There are two types of tubercular epididymis—the acute and the chronic.

In the acute form the onset is rapid and the epididymis and testicles are quite tender and feel very hard and there is some hydrocele present. If the patient has ever had gonorrhea, the diagnosis of gonorrheal epididymitis will probably be made. It is only by observing the patient that the true diagnosis finally becomes apparent. Instead of subsiding it may go on to suppuration or it may enter into the chronic type.

In the chronic form the onset is very insidious, the patient accidentally noticing that one testicle is larger than the other. The swelling may develop spontaneously, or it may follow an injury or be the sequel of a gonorrheal epididymitis. The epididymis on palpation will be found to be enlarged, nodular at either end or throughout the entire organ. It may be tender to palpation, but pain is rarely complained of. If the testicle is involved, nodulations or a hard, firm enlargement may be noticeable. At times, owing to marked hydrocele formation, the scrotal contents are obscured and cannot be palpated. The vas deferens will be enlarged, nodular and thickened. Rectal examination will usually reveal involvement of the prostate and seminal vesicles; and if the posterior urethra or bladder are involved, urinary symptoms and signs will be present. The disease may remain stationary for many months, but usually it gradually progresses. The nodulations soften, owing to abscess formation, and adhesions between the skin and epididymis will be evident. Finally the abscess bursts, and discharges a thick cheesy substance. Resulting fistulous tract formation is a sequel, and the latter tends to persist more or less indefinitely. The fistulæ are usually to be found at or near the lower pole of the organ. Their presence, as already noted, is one of the most important diagnostic points that we can obtain. The discharge from them may be slight or profuse, and the material is thin and yellowish in color. As already stated, there is a marked tendency of the disease to attack both sides and the operation of epididymectomy does not offer much protection to the opposite side, when the infection to begin with is unilateral. In the great majority of cases, the other side is attacked during the following six or twelve months (56 per cent. [Barney]). After that, the tendency to relapse drops steadily, but may take place after the expiration of eight years.

General or Constitutional Symptoms.—A patient may have both testicles and epididymes indurated, knotty and fistulous and yet enjoy excellent general health. The large majority, however, will give a history of loss of weight and show other evidence of tuberculous toxemia.

Treatment.—The treatment may be divided into conservative or radical.

Conservative Treatment.—Many authorities are of the opinion that conservative surgery with hygienic and dietetic methods of treatment offer the best results in the majority of cases. They maintain that radical removal of one epididymis and testicle encourages a recurrence of the disease on the opposite side. The psychic and moral effect of this catastrophe in many patients is a most serious and appalling matter. On this account, medical measures should first be given a thorough trial, and surgery limited to epididymectomy or incision and drainage of suppurating foci.

Medical Measures.—The patient should receive the same **hygienic, dietetic and climatic measures** that are given in **phthisis**. The results will be equally as favorable. Tuberculin treatment in the manner described under the treatment of Renal Tuberculosis offers the most valuable adjunct. Tonics such as **iron**, **arsenic** and **cod-liver oil** are efficient agents. The patient should wear a well-fitting **suspensory** or **jock strap**. Local remedies are useless. Under this régime, the patients are very often bettered or the process is at least stayed. Hydrocele, if small, should be left alone; if large, tapped. If the urine is infected, **sandalwood oil capsules** (minims x t. i. d. p. c.) should be administered. If the disease progresses notwithstanding palliative treatment, and fluctuating abscesses form, **incision** and **drainage** should be carried out or epididymectomy may be performed. Castration should only be carried out in the cases where the testicle has already been entirely destroyed by suppuration or in the very hyperacute form of tubercular orchitis. By conserving the testicle, even if at operation it shows foci of tubercular deposit, it may succeed in completely throwing off the tubercular disease and return to a more or less normal state. Following this line of treatment the tubercular vesiculo-prostatitis often recedes and becomes cured.

Radical Treatment.—The treatment practiced by Whiteside and Young in this country consists in the **radical excision of nearly the whole seminal tract**, *viz.*, both vesicles, both vasæ and both epididymes (epididymo-vaso-vesiculectomy). This operation has not met with general favor among the majority of urologists.

To recapitulate, the best treatment of tuberculosis of the genital tract is conservative and should be by methods which will increase the resistance and immunity of the individual. This is best accomplished by hygienic, dietetic and climatic measures, together with the judicious administration of tuberculin and drugs, such as iron, arsenic, cod-liver oil, sandalwood oil, etc. Urotropin and its compounds do more harm than good. If these fail, conservative surgery may be employed as an adjunct and radical surgery should be limited to those cases presenting serious complications, *e. g.*, extensive caseation, suppuration, or fistulization.

Prognosis.—The prognosis, as a rule, is rather gloomy. The vast majority of the cases succumb within a period of six years. The deaths usually occur from lung or renal involvement, or miliary tuberculosis supervenes. A patient may have relapses as long as eight years and cannot feel safe until the expiration of this time.

Tuberculosis of the Urethra

Tuberculosis of the urethra as a primary affection does not occur. As a disease secondary to other foci in the genito-urinary tract it may occur but rather rarely. However Pelouze in 1917 showed that the lesion was rather common in the posterior urethra.

Symptoms and Diagnosis.—Chronic urethral discharge, burning pain in the fossa navicularis during urination, or pain felt at the vesical neck are present. Pelouze claims to be able to diagnose tuberculosis of the posterior urethra, by the appearance through the urethroscope of lymphoid masses from one to three millimeters in size. They are found on the lateral walls of the posterior urethra, and appear paler than the urethral mucosa. Others have reported the characteristic ulcerations of tuberculosis not only in the posterior urethra but in the anterior urethra as well.

Treatment.—This is the same as for vesical tuberculosis (*q. v.*).

Tuberculosis of the Glans Penis

Tuberculosis of the glans penis is relatively rare. It is usually secondary to a focus elsewhere in the genito-urinary tract. For example, the author, in one case, in order to perform cystoscopy and ureter catheterization in a case of renal tuberculosis, had to slit the urinary meatus (meatotomy), in order to facilitate the introduction of the cystoscope. A short time later, the patient developed a very resisting tuberculous ulcer of the glans penis immediately about the meatal lips. A number of cases of tuberculosis of the glans penis have been reported following circumcision. Neuman has recorded 6 cases in children infected with tuberculosis, done in the course of six months by the same Jewish rabbi. A number of similar cases have been seen by Finney. While experimentally it has proven possible to produce tuberculosis of the glans by inoculation, no definite cases of tuberculosis of the glans penis have been proven contracted from coitus. A few cases are on record in which the disease seems to have been contracted through sexual intercourse, but each one seems to lack positive and indisputable proof. Walker has shown, however, that the penis in rabbits may be readily infected if a small wound is present. The possibility of local infection from coitus, therefore, must be granted.

Symptoms.—These are none other than an ulcer highly resistant to all forms of treatment.

Diagnosis.—This is made by microscopic sections and the presence of tuberculous lesions elsewhere in the genito-urinary tract.

Treatment.—**Remove the primary focus,** if possible. **Phenol** applications should be made locally, and the general treatment for genito-urinary tuberculosis may be used elsewhere.

BIBLIOGRAPHY

Barney, J. D. Tubercular epididymitis; end results of seventy-one cases. Boston Med. and Surg. Jour., 1922, clxvi, 409.

————. The ultimate results of genital tuberculosis in the male. Jour. Amer. Med. Assoc., 1914, lxiii, 2274.

————. Surg. Gynec. and Obstet., March, 1914, xviii, 307.

Cabot, H. Modern Urology, 1918, Vol. I, Lea & Febiger, Philadelphia.

Chetwood, C. H. The Practice of Urology, 1921, 3rd Ed., W. Wood & Co., New York.

Coleman, C. A. Tuberculin in the treatment of genito-urinary tuberculosis. Ohio State Med. Jour., 1913, ix, 227.

Creasy, R. Genito-urinary tuberculosis treated with massive doses of tuberculin. The Lancet, London, 1920, i, 542.

Colston, J. A. C., and Waters, C. A. The rôle of the x-ray in the diagnosis of long-standing renal tuberculosis. Johns Hopkins Hosp. Bull., 1919, xxx, 268.

Delagenière, M. Extirpation de la muqueuse vesicale pour tuberculose de la vessie. Ann. d. mal. d. org. genito-urin., Paris, 1896, xiv, 59.

Delli Santi, M. Sull' epididimite tuberculare primaria. Riforma Medica, 1903, xix, 925.

Halle, N. and Motz, B. Contribution a l'anatomiè pathologique de la tuberculose de l'appareil urinaire. Ann. de. mal. d org. genito-urinaries, 1903, xxi, 1041.

Hesse, F. A. Die Tuberkulose der Prostata. Centrale bl. f. d. Grenzgeb. de. Med. und Chir., 1913, xvii, 297.

Kappis, M. Experiments über die Ausbreitung der Urogenitaltuberkulose bei Sekretstanung. Arb. d. Geb. d. path. Anat. Inst. zu. Tübing, 1906, v, 379.

Keyes, E. L. Tuberculosis of the testicle. Ann. Surg., 1907, xlv, 918.

————. Diseases of genito-urinary organs, 1910, D. Appleton & Co., New York, N. Y.

Kolischer, C. Clinical relations of the female bladder to the other organs. Urologic and Cutaneous Review, 1920, xxiv, 185.

Kraemer, C. Ueber die Ausbreitung und Entstehungsweise der männlichen Urogenitaltuberkulose. Deut. Zeit. f. Chir., 1903, lxix, 318.

————. Experimentelle Beiträge zum Studium der Hodentuberkulose. Wien. med. Wchnschr., 1900, l, 2121.

Krzywicki, C. Neunundzwanzig Fälle von Urogenitaltuberkulose, darunter ein Fall von Tuberkulose beider Ovarien. Beitr. z. path. anat. u. z. allg. Path., Jena, 1888, iii, 295.

Mukharinski, M. A. Specific diagnosis and therapy of tuberculosis of genito-urinary organs. Novoye v. Med., St. Petersburg, 1913, vii, 449.

O'Neill, R. F., and Hawes, J. B. Remarks on the rational treatment of genito-urinary tuberculosis. Am. Assoc. Genito-urin. Surg., 1913, viii, 113.

Paladino-Blandini, A. La tuberculose de l'epididyme dans ses rapports avec le mode de propagation des micro-organismes le long des voies de l'appareil uro-genital. Ann. des mal. des org. genito-urinaries, 1900, xviii, 1009.

Pinaud. Cited by Seifert. Beitrag zur Tuberkulose der ausseren Genitalein des Mannes. Dermatologische Studien, 1910, xx, 113.

Pelouze, P. S. Lymphoid and cystic bodies in the urethra as an evidence of tuberculosis. Journal Urology, 1917, I, 367.

Reclus, P. Du tubercule du testicule et de l'orchite tuberculeuse. Thèse de Paris, 1876.

————. Tuberculosis of the genito-urinary tract. Thèse de Toulouse, 1899.

Ribbert, M. W. H. Ueber die Ausbrietung der Tuberkulose im Körper. N. G. Elwert, Marburg, 1900.

Rovsing, T. Urogenital tuberkulose. Bibliot, f. Laeger, Kjbenh., 1918, cx, 17.

————, Om Blaerebetaendelsemes aetiologi Pathogenese og Behandling (cystitis). Kjbenh., 1889, P. Hamberg & Co., 1889.

Rytina, A. B. Renal tuberculosis. Annals of Surgery, 1917, lxv, 346.

Smith, J. Clinical lecture on genito-urinary tuberculosis. Australian Med. Jour., 1913, ii, 1027.

Sugimura, S. Experimente über den Ausbreitungs-modus der Tuberkulose im Harnund männlichen Geschlechtsorganen. Arb. a. d. Geb. d. Path. Anat. u. Bakt. Inst., 1912, viii, 1 and 41.

Uchimura, M. Tubercular disease of genito-urinary organs seen from postmortem examination. Sei-I-Kwai Med. Jour., 1914, xxxiii, 30.

Walker, G. Studies in the experimental production of tuberculosis in the genito-urinary organs. Johns Hopk. Hosp. Bull., 1911, xvi, 1.

WALKER, K. M. Hunterian lecture on the paths of infection in genito-urinary tuberculosis. Lancet, 1913, i, 435.

WATSON, F. S., and CUNNINGHAM, J. H. Genito-urinary diseases, 1908, Lea & Febiger, Philadelphia and New York.

WHITE, J. W., and MARTIN, E. Genito-urinary surgery and venereal diseases, 1920, 12th ed. rev., J. B. Lippincott Co., Philadelphia and London.

WHITESIDE, G. S. The use of tuberculin in treatment of surgical urogenital tuberculosis. Jour. Amer. Med. Assoc., 1912, lix, 2232.

————. Radical surgery in advanced genital tuberculosis. Amer. Assoc. Genito-urinary Surg., 1914, ix, 173.

WILLIAMS, J. W. Tuberculosis of the female generative organs. Johns Hopkins Hospital Bulletin, 1892, iii. 85.

YOUNG, H. H. The radical cure of tuberculosis of the seminal tract. Arch. Surg., March, 1922, iv, 334.

CHAPTER LII

BRONCHOPNEUMONIA

By Arthur L. Bloomfield, M.D.

Synonyms, p. 391.
Definitions, p. 391.
Etiology, p. 392:—Predisposing causes, p. 392; Mechanical injuries, p. 392; Thermal injuries, p. 393; Chemical injuries, p. 393; Infection, p. 393; Association with other diseases, p. 394; Exciting causes, p. 394; Mode of conveyance of disease, p. 396.
Symptomatology, p. 396:—Primary bronchopneumonia, p. 398; Bronchopneumonia following acute infectious diseases such as measles and influenza, p. 398; Bronchopneumonia following previous pulmonary infection such as bronchitis, p. 399; Bronchopneumonia associated with localized lung lesions such as tumors and cysts, p. 400; Metastatic bronchopneumonia during the course of septic infection, p. 400; Intercurrent and terminal bronchopneumonia, p. 401; Laboratory findings, p. 401; Special examinations, p. 402; Bronchoscopy, p. 403; Vital capacity, p. 403.
Diagnosis, p. 403:—Sputum culture, p. 403.
Complications and sequelae, p. 403.
Treatment, p. 404:—General prophylaxis, p. 404; Individual prophylaxis, p. 405; Vaccines, p. 405; General treatment, p. 405:—Observations, p. 405; Regulation of patient's activity, p. 406; Nursing care, p. 407; Fresh air, p. 407; Diet, p. 407; Fluids, p. 408; Care of bowels, p. 408; Hydrotherapy, p. 409; Drugs, p. 409:—Symptomatic treatment, p. 409; Pleural pain, p. 409; Cough, p. 409; Dyspnea, p. 410; Restlessness, insomnia and apprehension, p. 410; Delirium, p. 411; Circulatory failure, p. 411:—Specific therapy, p. 412; Isolation, p. 412; Treatment of complications, p. 413:—Empyema, p. 413; Abscess, p. 414:—Convalescence, p. 415.
Prognosis, p. 415.
Pathology, p. 415.

Synonyms.—Lobular pneumonia, catarrhal pneumonia, capillary bronchitis.

Definition.—A simple definition of bronchopneumonia is difficult, since, unlike such diseases as typhoid fever or acute lobar pneumonia the bronchopneumonias comprise a group of conditions of widely differing etiology, pathology and course. The term is usually applied, however, to an inflammatory process in the lung consisting of multiple diffuse or focal lesions primarily or secondarily associated with the presence of infectious microörganisms and, whatever its origin, eventually involving the actual lung parenchyma.

The main value of the word "bronchopneumonia" lies perhaps in its implication of a condition different from acute lobar pneumonia—a disease of distinct etiology and pathology; and inasmuch as all "bronchopneumonias" by no means result from extension of a bronchial infection the term should not be regarded as accurate from a descriptive anatomical standpoint.

Etiology.—When one considers that the lungs are contiguous to the upper air passages which are inhabited by a host of microörganisms, that at every inspiration dust and droplets may be inhaled, and that all the blood in the body rapidly passes through the lesser circulation with consequent ready accessibility of the pulmonary tissue to bacteria brought from other regions, it is to be expected that under appropriate circumstances infection of the lung should result. It is not remarkable then, that the bronchopneumonias are found to arise under a variety of conditions and that they are caused by many diverse types of injury.

In practically every case the lesion is associated with the presence of bacteria. However, predisposing causes are of such importance that the etiology must be discussed both from the bacteriological standpoint and from the standpoint of injuries which prepare the way for later infections.

PREDISPOSING CAUSES.—As might be expected in the case of a nonspecific group of conditions such factors as race, sex, soil, altitude, and diet *per se* play little or no rôle in causation. There are, however, definite types of injury which lead to the occurrence of bronchopneumonia. Such injuries may be classified as mechanical, thermal, chemical and infectious.

MECHANICAL INJURIES.—Bronchopneumonia occasionally may follow an injury to the chest. It may be assumed that an area of lowered resistance has been created in the lung which becomes infected by chance invaders when normal tissue would escape. The great group of terminal and hypostatic pneumonias which occur almost invariably in individuals debilitated or bed-ridden for long periods of time are undoubtedly due in part to the mechanical factor of relaxed and unexpanded lung tissue which lends itself readily to infection. In a similar way foreign bodies in the lung (even if primarily sterile), tumors, and cysts are prone to set up a reactive inflammation about themselves; in addition they will be aided by the ubiquitous organisms which are always ready to take advantage of injured tissue. To this group finally should be added the cases of so-called aspiration pneumonia. In health the lungs are protected against the entry of foreign particles and bacteria by an effective mechanism whose action depends upon the integrity of the mucosa of the upper air passages and on the normal function of the respiratory and deglutition reflexes. Abolition or depression of these reflexes by exhaustion, anesthesia, coma, operations on the mouth or nose, diseases of the pharynx, larynx or esophagus, or experimentally by section of the vagi is often followed by aspiration of infected particles of food, vomitus or other foreign matter with consequent bronchopneumonia. An interesting group of cases follows submersion. One may also include at this point the bronchopneumonia arising by direct extension from an inflammatory process below the diaphragm, as in the case of rupture of a liver abscess, or from the esophagus, especially by perforation of a carcinoma, or from the aspiration of material from other parts of the lung itself as in bronchiectasis, ruptured empyema, or after hemoptysis. In many of these conditions infection as well as mechanical injury is of primary importance.

THERMAL INJURIES.—There is an old and deeply-rooted tradition in medicine that cold is a predisposing factor to infection. The ultimate validity of this assertion remains unproved, but a host of clinical observations seem to support the idea. The recent thorough experiments of Mudd and his associates appear, however, to bring some real evidence that thermal variations lead to marked vasomotor and secretory disturbances in the upper air passages. These workers also found that the bacterial flora may be modified following such reactions. It seems altogether probable then that certain instances of bronchopneumonia are related to undue exposure to cold and inclement weather, at least in so far as such exposure may let down the bars to bacterial invasion.

CHEMICAL INJURIES.—Chemical injuries may alter the normal protective reactions so that the lung becomes accessible to infection. Three prominent examples may be quoted: War-gas poisoning if of any degree of severity is followed by bronchopneumonia, and histologic studies of the tissues show the bacteria actually invading the mucous surfaces denuded of their protecting epithelium; poisoning with certain arsenicals allied to arsphenamin is accompanied by a severe erythema of the respiratory tract mucosa, and is soon followed by a bronchopneumonia clearly secondary to the chemical injury; and ether anesthesia may be followed by pneumonia, which probably results from chemical irritation together with infection.

INFECTION.—Infectious diseases make up by far the most important group of causes which predispose to bronchopneumonia. Measles, scarlet fever, diphtheria, small-pox, influenza, dysentery, and typhoid fever are all familiar examples. The rôle of the exanthemata in this regard is notable. Measles especially is likely to be followed by pneumonia, and the influenza pandemic of 1918-19 drew its deaths almost entirely from the complicating pulmonary infections. The erythema of the respiratory mucosa in this disease is probably associated with a disturbance of the normal protective mechanism following which secondary infections with various organisms readily occur. Olitsky and Gates bring suggestive experimental support for this idea in the case of influenza.

Previous infections of the respiratory tract are of the utmost importance, and the physician is daily called on to decide whether a simple bronchitis has advanced to the point of involving the actual lung parenchyma—namely bronchopneumonia. Furthermore, local infections in remote parts of the body—such as osteomyelitis, puerperal infection, sinus phlebitis, endocarditis, and many others—during the course of which bacteria are conveyed to the lungs, may be followed by bronchopneumonia.

The above outline indicates the wide variety of possible predisposing causes of bronchopneumonia but is by no means a complete list. Under appropriate conditions more indefinite factors seem to bear a distinct relationship to the disease.

Season in a general way is of importance, since upper respiratory tract infections and the infectious diseases which may be followed by bronchopneumonia occur most frequently in the fall, winter, and early spring months. Furthermore individuals with chronic bronchitis, emphysema and bronchiectasis are notably subject to exacerbations during the inclement months of the year.

Age is a factor, as young children and old people, other things being equal, are very likely to develop bronchopneumonia, perhaps owing to the frequency of chronic bronchial infections and debilitating conditions in the latter and serious nutritional disturbances in the former. Poor hygienic conditions and, above all crowding, clearly predispose to bronchopneumonia under certain circumstances. The tremendous epidemics in the military camps in 1918-19 were undoubtedly connected in some way with the concentration of large numbers of individuals under strange and trying conditions.

ASSOCIATION WITH OTHER DISEASES.—This point has already been touched upon, but one should stress the frequent and close relationship of bronchopneumonia to certain other pulmonary conditions, namely, acute bronchitis, chronic bronchitis, emphysema and bronchiectasis. It is readily seen in these cases that infection may from time to time extend to the actual lung parenchyma.

EXCITING CAUSES.—In all instances of bronchopneumonia the actual exciting cause is some form of microörganism, and a complete list would probably demand the enumeration of most of the bacteria concerned in human disease. Furthermore, several or many organisms may coëxist in the lesion, leaving the examiner in some doubt as to the one of major importance.

At this point a word may be said as to the rôle of primary and secondary infection in bronchopneumonia, a question which daily comes up for discussion in the clinic as well as in the literature. By a primary infection one usually means the invasion of a previously healthy tissue —a virgin soil—by organisms which proceed to unfold their activities at the site of inoculation; by a secondary infection one means the entry and growth of bacteria in a region already damaged by preceding infection or injury. In a general way it has been assumed that bronchopneumonia is usually secondary whereas lobar pneumonia is more likely to be a primary infection. In neither instance, however, does the question at present seem capable of final proof. Perhaps the most useful approach for the practitioner is to study the clinical associations of the condition under observation; a bronchopneumonia following measles is certainly secondary; a bronchopneumonia coming out of a clear sky in a previously healthy individual is perhaps best regarded as primary, at least from the clinical standpoint. Purely academic discussions in this connection are unprofitable.

To return then to the problem of etiology the mere nature of the organism found in the lung does not settle the question of the primary or secondary character of a bronchopneumonia. But from the standpoint of the bacteriological findings the bronchopneumonias may logically be divided into two groups: (1) Bronchopneumonia occurring during the course of an infection with a specific organism and caused by these same organisms, such as the bronchopneumonias of tuberculosis, plague, diphtheria and septic infections, and (2) bronchopneumonia, whether primary or secondary, which is caused by an organism not otherwise an essential feature of a previous disease process. As stated above the bacteria included in the second group are numerous but certain ones stand out as occurring with special frequency. This group includes especially those organisms which are common inhabitants of the upper passages, to wit: Streptococci (both hemolytic and green-producing), pneumococci, influenza bacilli, staphylococci, Gram-negative cocci, and diphtheroid bacilli of various kinds.

BRONCHOPNEUMONIA—ETIOLOGICAL FEATURES

Predisposing Causes

(Injury With or Without Infection)

Mechanical Injuries

Trauma.
Foreign body in lung.
Tumors and cysts of lung.
Aspiration of foreign particles of infected material.
Disturbance of respiratory reflexes in anesthesia, coma, etc.
Submersion.
Rupture of abscess into lung.

Thermal Injuries

Exposure to cold.

Chemical Injuries

Gas poisoning.
Inhalation of other irritants.

Infectious Diseases

Contagious diseases of childhood.
Small-pox.
Influenza.
Dysentery.
Typhoid, etc.

Season

Fall, Winter, Spring.

Age

Infants and old people.

Hygienic Conditions

Overcrowding.

General Causes

Cachexia.
Wasting or debilitating diseases.

Exciting Causes

(Pathogenic Microörganisms)

May produce bronchopneumonia by primary infection or may be secondary to one of the predisposing causes.

*Aërogenous Infection**

(Usually)

Streptococcus.
Pneumococcus.
Influenza bacillus.
Gram-negative cocci.
Tubercle bacillus.
Plague bacillus.
Diphtheria bacillus.
Staphylococci
Yeasts.
Spirochetes and many other bacteria.

*Hematogenous Infection**

(Usually)

Pyogenic cocci.
Members of the typhoid-colon group, and many other bacteria.

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* No rigid distinction between two groups.

The bacteriological findings vary furthermore with the mode of invasion of the lungs. The vast majority of cases are probably aërogenous infections, whether the organisms reach the actual lung tissue by the air currents or come from the upper air passages by way of the lymphatics —a route which has been pointed out by Winternitz and by Blake—and in this case the flora encountered is usually that included above in Group 2. On the other hand when the exciting cause reaches the lung through the blood stream, as in instances of septic infection, the organism is likely to be that which is producing the general disease.

In summary, then, the main etiological features of bronchopneumonia may be arranged as in the foregoing table.

Mode of Conveyance of the Disease.—Under certain special circumstances bronchopneumonia may become epidemic. Usually in connection with crowding or concentration of large numbers of individuals under relatively unfavorable hygienic conditions some organism or group of organisms may be rapidly spread from person to person with consequent high incidence of disease. This was beautifully illustrated by the bronchopneumonia of the Army Camps. Following the epidemic of measles and of influenza came cases of secondary bronchopneumonia often due to hemolytic streptococci. Eventually these organisms seemed to become so exalted in virulence that epidemics of bronchopneumonia which clinically, at least, were primary occurred in association with them.

Under ordinary conditions, however, bronchopneumonia must be regarded as essentially an autogenous infection. As pointed out above, the majority of cases are due to bacteria already present in the upper air passages or elsewhere in the body which are enabled to take advantage of lowered resistance in the lung to set up disease.

It is clear that bronchopneumonia cannot be limited or prevented by the application of any single principle of prevention such as carrier control; special precautions as will be indicated later must be employed according to the particular existing conditions.

Symptomatology.—Clinical History and Physical Findings.—Inasmuch as bronchopneumonia is usually an incident in or the conclusion of a preceding disease process the symptomatology is complex. The physician must carefully distinguish, for example, between uncomplicated measles, influenza, and bronchitis, and the cases in which secondary infection has involved the actual lung parenchyma. In people ill with chronic or wasting diseases or in old bed-ridden patients the actual onset of bronchopneumonia is often so insidious as quite to defy exact chronological definition.

But in a typical case of apparent primary bronchopneumonia the picture is fairly clean-cut. An individual, perhaps previously in good health, is taken with the constitutional reactions of an acute infectious disease. The onset is often sudden but rarely as fulminating as that seen in acute lobar pneumonia. Within a few hours or a day or so the patient becomes definitely conscious of lack of well being, there are chilly sensations or definite chills, malaise, prostration, aching and fever. This reaction usually precedes the localizing symptoms which, however, are often evident within the first day or two,—namely, cough, dyspnea, perhaps pain in the chest, and expectoration. If an examination is made within the first twenty-four hours there is usually little to be made out physically save the general evidences of an acute febrile disease—prostration, fever, and rapid pulse. The examiner is often in doubt although his attention may be called to the lungs by the appearance of cyanosis, acceleration of respirations, and the presence of slight impurity of the breath sounds with a few fine râles over one or more areas, especially in the lower lobes. During the succeeding few days it usually becomes evident that there is trouble in the lungs. Cyanosis, with a certain amount of pulmonary distention and lowering of the vital capacity, is likely to occur and the respirations are almost always slightly accelerated, though one does not as a rule see the extremely rapid and labored breathing with use of the accessory muscles which is common in acute lobar pneumonia. Cough increases and yields sputum which is characteristically greenish and mucopurulent in contra-distinction to the tenacious rusty discharges of pneumomoccus lobar pneumonia. The evolution of the physical signs in the lungs is as follows: Without sudden or extensive percussion changes there appear areas of greater or of lesser extent over which the breath sounds are faint and impure and are accompanied by showers of coarse and fine râles. The signs may never progress beyond this point or the breathing may become bronchovesicular or outspokenly tubular indicating the occurrence of relatively large areas of solidification.

Unlike lobar pneumonia the duration of a bronchopneumonia is indefinite. The fever and pulse rate may fall to normal within a few days with rapid clearing of the physical signs or the process may keep up for weeks or months. In the prolonged cases the fever may be continuous, suggesting the curve of typhoid fever, or it may be irregular often with the high point in the evening. As the infection progresses the pulse tends to become more rapid. The physical signs in the lungs may remain remarkably constant over long periods of time or they may resolve in one part of the chest as they develop elsewhere.

Aside from the above there is little characteristic in the physical examination, the other findings depending upon the nursing care and general severity of the reaction. Neglected cases show a dry coated tongue, abdominal distention, and poor mental condition or morale, but such features are not essential to the disease.

Recovery is regularly heralded by general improvement and fall in temperature and pulse rate. The physical signs, especially areas of impure faint breath sounds and râles, or cough with a certain amount of sputum, persist notably after the patient is otherwise well. In certain cases the signs are permanent and are associated with recurrences at greater or shorter intervals.

This brief description by no means completes the picture of bronchopneumonia. As indicated, the disease is most protean in its manifestations and indeed, can hardly be fitly considered without the actual setting in which it is seen under various conditions. It is necessary, therefore, to present actual instances of the most important clinical types of bronchopneumonia in order to bring out more clearly the various kinds of reaction.

PRIMARY BRONCHOPNEUMONIA.—Bronchopneumonia occurs not infrequently as a primary conditiion, at least without any clinically recognizable antecedent or coincident disease. The pneumonias of infancy fall largely into this group. The following case illustrates this type:

CASE HISTORY.—Bronchopneumonia, primary in a healthy adult. Duration several weeks with high fever, cough, sputum, dullness, râles and impure breath sounds, gradual resolution and recovery.

C. K. (Medical No. 48320), aged 34, white, male, groceryman was admitted to the Johns Hopkins Hospital on October 12, 1922, and was discharged on November 3, 1922.

Family History.—Unimportant.

Personal History.—Health good. No previous respiratory tract infections.

Present Illness.—Onset after previous good health on September 15, 1922, with headache, fever, weakness, fatigue, drowsiness, anorexia and constipation. The symptoms were not fulminating but there was definite departure from health within a few hours. Within twenty-four hours of onset he began to have slight cough with pain over the midsternum and the left border of the chest with small amount of greenish suptum. There was no respiratory distress or hemoptysis. Condition remained essentially unchanged for about three weeks when he entered the hospital.

Physical Examination.—On entry examination showed a fairly well-nourished man who looked sick and febrile. There was frequent cough with expectoration of large amounts of light greenish mucopurulent sputum. The temperature was 104° F. (40° C.), the pulse 90, the respiration 24 per minute. Over the lower half of both lungs the breath sounds were impure and faint and there were showers of fine and medium moist râles. For about a week the condition remained essentially unchanged, and the temperature persisted at from 102° to 104° F. (38.8° to 40° C.). During the following four days it gradually fell to normal, and coincidently the pulmonary signs decreased. He did not seem very ill at any time, there was no dyspnea or cyanosis, and on October 24th, about seven weeks after onset, he was discharged. At that time there were still a few crackles at both bases.

Laboratory Findings.—White blood-cells, October 12, 1922, 6,400; polymorphonuclear neutrophil 83 per cent.; sputum (repeated examinations) abundant, green, mucopurulent. Culture—Pneumococcus Type II.

X-ray Report.—October 12th, lungs clear; October 23, lungs clear.

Final Diagnosis.—Bronchopneumonia (Pneumococcus Type II).

Summary.—A case of primary bronchopneumonia due to a Type II pneumococcus, duration about seven weeks with cough, sputum, high fever, suppression and râles in the lower lobes, absence of leukocytosis or of striking x-ray changes.

BRONCHOPNEUMONIA FOLLOWING ACUTE INFECTIOUS DISEASES SUCH AS MEASLES AND INFLUENZA.—This group of cases is one of great frequency and importance, the pulmonary complication usually being directly responsible for death. The following case is typical:

CASE HISTORY.—Epidemic influenza in a healthy young adult. On fourth day development of fulminating extensive bronchopneumonia with collapse and death on eighth day.

E. G. (Medical No. 40477), age 34, white, male, physican, was admitted to the Johns Hopkins Hospital on October 4, 1918, and died on October 12, 1918.

Family History.—Unimportant.

Personal History.—Unimportant. Health always good. Physician in active work.

Present Illness.—Onset with slight coryza, October 2, 1918, during the pandemic of influenza. October 3rd and 4th, chilly sensations, severe headache, pain in eyeballs, general aching, malaise, and increasing prostration. No symptom referable to respiratory tract on entry October 4, 1918.

Physical Examination.—This showed the evidences of a severe but uncomplicated case of epidemic influenza. The temperature was 102° F. (38.8° C.), the pulse

100, and the respirations 16 per minute. There were marked prostration and an erythematous flush of the face and upper chest. The pharynx was dry and red. The lungs were clear. The leukocyte count was 2400; polymorphonuclear neutrophil 70 per cent.

From October 4th to 6th there seemed to be slight improvement. On October 8th, temperature rapidly rose to 105° F. (40.5° C.) and the respirations to 26 per minute. The patient became delirious. There was increasing cough and dyspnea with expectoration of a moderate amount of thin fluid brick-red sputum. The leukocytes rose to 4500. On October 9th there were râles throughout both lower lobes, and on October 10th there were frank signs of consolidation of the left lower lobe and later of right lower and middle lobes. On October 11th he was much worse; he seemed worn out. He was alert but flighty and rambling; he had a short catchy cough, and friction rub in left axilla. There was rapid failure during the night; he presented high fever and a rapid feeble running pulse. There were râles throughout both lungs. Collapse and coma ensued and death came at 10 A. M., October 12, 1918.

Sputum Culture.—Hemolytic streptococcus.

Autopsy.—Bilateral confluent bronchopneumonia in both lower lobes; beginning bronchopneumonia in upper lobes; fibrinous pleurisy.

Summary of Case.—Epidemic influenza complicated by severe pseudo-lobar bronchopneumonia due to infection with hemolytic streptococcus; death. The absence of leukocytosis is of interest.

BRONCHOPNEUMONIA FOLLOWING PREVIOUS PULMONARY INFECTION SUCH AS BRONCHITIS.—This group includes cases of great importance inasmuch as an attack of bronchopneumonia superadded to previous pulmonary infection may be the final burden which overcomes the patient. Chronic bronchitis, emphysema, and bronchiectasis are important preceding lesions to the bronchopneumonia. The following case is one in which all three lesions were present:

CASE HISTORY.—Chronic bronchitis of years' standing in a young individual followed by emphysema and diffuse bronchiectasis. Repeated attacks of bronchopneumonia. Secondary dilatation of right heart. Myocardial insufficiency. Death.

K. G. (Medical No. 39201), aged 19, white, female, factory worker, was admitted to the Johns Hopkins Hospital on March 16, 1916, and died on May 20, 1916.

Family History.—Unimportant.

Personal History.—Frequent attacks of "bronchitis" in early childhood. These increased in frequency and since the age of thirteen she has had practically constant cough all winter. There is a history of profuse expectoration at times amounting to a pint in twenty-four hours. During the past two winters she has had attacks of "asthma" during which she becomes extremely short of breath, the difficulty being both inspiratory and expiratory. Last winter during one of these attacks there was swelling of the legs.

Physical Examination.—On entry to the hospital the patient seemed *in extremis.* There was very marked orthopnea with stridor and extreme cyanosis, the lips and ears being a dark purple color. There was edema of the legs and the liver was swollen and tender. The chest was emphysematous, practically fixed in the inspiratory position and both lungs were filled with coarse, moist and piping and squeaking râles. The heart was markedly enlarged. Temperature 103° F. (39.4° C.). Pulse 140 per minute. Respirations 36 per minute. Following venesection, rest in bed, digitalis, inhalations and drainage her condition gradually improved. The evidence of cardiac failure disappeared, the cough became less and the temperature fell to normal save for slight evening rises. There were, however, persistent râles throughout both lungs and at times areas of bronchovesicular breathing were present. The leukocytes varied from 12,000 to 18,000.

X-ray Examination.—X-ray of chest showed large dilated heart, marked exaggeration of the root shadows, especially in the lower lobes with small dense areas which were regarded as patches of bronchopneumonia.

On May first condition again became worse and despite active treatment there was increasing exhaustion, the evidences of cardiac failure, and finally death in coma.

Sputum Culture.—This showed Pneumococcus Type IV and Bacillus influenzæ.

Autopsy.—Cardiac dilation and hypertrophy especially of the right heart, congestion of viscera, chronic bronchitis, emphysema, diffuse cylindrical bronchiectasis and bronchopneumonia.

Summary.—An instance of long-standing pulmonary infection (chronic bronchitis with emphysema and bronchiectasis), secondary cardiac changes owing to obstruction in the lesser circulation, myocardial insufficiency, repeated attacks of bronchopneumonia with death during an attack.

BRONCHOPNEUMONIA ASSOCIATED WITH LOCALIZED LUNG LESION SUCH AS TUMORS AND CYSTS.—This group includes many cases of great importance from the standpoint of diagnosis as the underlying condition may be masked by bronchopneumonia. This is a common experience in the case of lung tumors. The following case is illustrative:

CASE HISTORY.—Echinococcus cyst of lung presenting as a case of bronchopneumonia. Diagnosis of cyst made after acute pulmonary process had cleared up.

P. S. (Medical No. 36135), age 24, white, male, confectioner. Was admitted to the Johns Hopkins Hospital on May 22, 1916 and discharged on July 8, 1916.

Family History.—Unimportant.

Personal History.—Patient was born in Greece where he lived until coming to this country four years ago.

Present Illness.—In December, 1915, after previous perfect health, the patient had an acute respiratory infection of some sort with cough, sputum and severe pain referred to right lower chest. He has been weak ever since with persistent slight pain in right side and some shortness of breath on exertion. Two days ago there was a huge hemoptysis which was the immediate cause of his entry into the hospital.

Physical Examination.—The patient was brought in on a stretcher. He was in collapse, extremely weak and pale. The blood count showed red blood-cells 2,300,000, hemoglobin 50 per cent. and white blood-cells 14,000. The movement of the right chest was limited. There were tympany and crackles with harsh breath sounds over the right lower lung. The temperature was 104° F. (40° C.), pulse 120, and respirations 32 per minute. During the next few days his condition remained essentially the same save that small areas of tubular breathing were made out over right lower lobe. There was a small amount of bloody sputum containing epithelial cells and cocci.

X-ray Examination.—The x-ray report on May 31, 1916, was as follows: Spotty infiltration of both uppers, pleurisy of the right lung with probably some consolidation in right lower.

A provisional diagnosis of an atypical bronchopneumonia was made. During the first ten days after entry, the fever gradually fell, the cough and sputum disappeared and the lung signs practically cleared except for a few crackles over the right lower lobe. Another x-ray was made which now showed (June 24, 1916) "A small round localized shadow in the right lower lobe with sharp outline, suggestive of cyst." Later on during another attack of hemoptysis the cyst membranes and hooklets characteristic of echinococcus were expectorated. The diagnosis was finally confirmed by operation.

Summary.—A case of echinococcus cyst with reactive bronchopneumonia masking at first the correct diagnosis.

METASTATIC BRONCHOPNEUMONIA DURING THE COURSE OF SEPTIC INFECTION.—During the course of septic infections such as osteomyelitis, suppurative pylephlebitis, puerperal infections, and endocarditis bacteria may be carried to the lung and set up a bronchopneumonia as illustrated by the following case:

CASE HISTORY.—Puerperal infection; colon bacillus septicemia; bronchopneumonia with colon bacillus in sputum in pure culture; recovery.

M. M. (Medical No. 39483), age 28, white, housewife, entered the Obstetrical Service of the Johns Hopkins Hospital on August 16, 1921, where she was delivered of a normal child. Symptoms of a severe puerperal infection developed within a few days with chills, sweats, fever, leukocytosis and uterine discharge in which the colon bacillus predominated. The blood culture yielded colon bacilli on August 28th, and frequently thereafter. On September 3rd there was sudden severe pain in right chest with dyspnea and cough and during the next few days the signs of a patchy consolidation developed at the right base. There was profuse greenish sputum which yielded colon bacilli in pure culture. For a month the patient was desperately ill with high irregular fever, frequent chills and sweats, and rapid pulse. The pulmonary signs cleared very gradually, the blood cultures became sterile and she was discharged well about three months after entering the hospital. The pulmonary process probably began with an infected embolus around which areas of bronchopneumonia developed.

INTERCURRENT AND TERMINAL BRONCHOPNEUMONIA.—One of the most common types of bronchopneumonia is that which occurs in patients ill with chronic or wasting diseases or in those who have been bed-ridden for long periods of time. Such pneumonias may arise as intercurrent infection from which the patient recovers but more usually they develop as a terminal event. Not infrequently their onset is so insidious and the reaction so slight that the condition is not recognized until revealed at autopsy. The following case illustrates the usual course of events:

CASE HISTORY.—Carcinoma of stomach; cachexia; terminal bronchopneumonia. A. N., white, female, aged 55, entered the Johns Hopkins Hospital on May 11, 1919, complaining of pain in stomach and vomiting. A large mass was felt in the epigastrium; there was emaciation, anemia, and the laboratory and x-ray evidences of cancer of the stomach. An exploration was performed which revealed an inoperable carcinoma of the pylorus and lesser curvature. Immediate recovery from operation uneventful. Steady failure. On June 16th there was a slight rise of temperature to 100° F. (37.7° C.). Examination showed moist râles in both lower lobes. There was no cough, sputum, acceleration of respirations or leukocytosis. On June 21st patient passed into coma, dying on the following day.

Autopsy.—Cancer of stomach, bronchopneumonia both lower lobes.

Summary.—A case of cancer of the stomach with insidious and practically latent terminal bronchopneumonia.

These cases illustrate the variability of the clinical picture of bronchopneumonia. It should be emphasized that the physical examination of the lungs cannot in itself be depended upon in making the diagnosis, inasmuch as frank signs of consolidation are so often lacking. Under suggestive conditions bronchopneumonia must be thought of even if the pulmonary examination is essentially negative, although in the vast majority of cases impurity of the breath sounds and râles at least are present.

LABORATORY FINDINGS.—The laboratory findings in bronchopneumonia like the clinical features are variable depending upon the associated conditions.

Blood.—Except in long-standing cases with wasting or septic poisoning the bronchopneumonic process itself exerts little or no effect on the red blood-cell count or hemoglobin content as determined by ordinary clinical examination. A secondary anemia of moderate degree may develop. The leukocyte count is usually elevated (10,000 to 20,000), but here again there are many exceptions and the blood-picture may conform to that expected in the predisposing disease. In severe cases of post-influenzal bronchopneumonia, for example, the leukopenia of the primary disease may persist. Study of the oxygen and carbon dioxid content of the arterial and venous blood shows interesting and important changes which explain some of the clinical findings. It has been found that marked grades of cyanosis may be due to lack of proper saturation of the blood with oxygen as it passes through the pneumonic lung and the degree of such unsaturation (Lunsgaard) may have some prognostic bearing.

Urine.—The urine shows no special features save those of an acute fever—high color, high specific gravity, and perhaps albumin and casts. In uncomplicated cases these findings usually disappear after fluids have been freely ingested.

Sputum.—Study of the sputum is of special importance. It contains presumably the exciting organisms and accurate diagnosis cannot be achieved without bacteriological study of the secretions. The sputa are variable in character. They may be small in amount or very profuse, amounting to several hundred cubic centimeters in twenty-four hours; they may be mucoid, mucopurulent, purulent, bloody, or foul, depending upon the exact nature and severity of the case. It may safely be said, however, that they never exactly resemble the typical tenacious rusty sputum of acute lobar pneumonia. Microscopic examination of the fresh expectorations reveals pus-cells, and perhaps blood-cells, mucus and detritus. In cases associated with gangrene of the lung elastic tissue fragments may be found. Stained smears (Gram's stain, methylene-blue) reveal bacteria among which one variety may often be recognized as predominating. Sputum culture, however, is the most important part of the examination (*v. infra* Diagnosis).

Blood Culture.—As a rule the blood is sterile. In severe cases which have led to a general sepsis bacteria usually enter the blood stream. Recovery of organisms in this way indicates an unfavorable outcome.

SPECIAL EXAMINATIONS.—*X-ray.*—The roentgenogram is of the greatest service in the intelligent study and care of bronchopneumonia. A foreign body in the lung may be revealed, as well as the degree and extent of the pneumonic process, the course of the lesion relative to healing, and the presence of complications and sequelæ such as empyema, bronchiectasis and abscess. The examiner must remember, however, that the x-ray plate shows not lesions but merely shadows corresponding to areas of relative density of the tissues.

In many cases of bronchopneumonia the x-ray shows little abnormal despite the presence of outspoken physical signs. This is especially so of the acute diffuse lesions in previously undamaged lungs. Here there may simply be inflammation of the finer bronchioles and their terminal cells with exudation of fluid, so that while dulness and râles are obvious to the clinician the roentgenologist notes nothing remarkable in the plate.

As a rule, however, the lesion is indicated either by patchy areas of increased density with exaggeration of the root markings or by large dense shadows corresponding to extensive areas of solidification. Even in extreme cases one rarely sees the large clearly defined shadows which appear in full-blown cases of lobar pneumonia, although final differentiation by x-ray is difficult.

Resolution is usually evident by a patchy, or mottled appearance in the plate corresponding to the area of involvement and in an upper lobe this may closely simulate the radiographic appearance of tuberculosis. Some clouding and intensification of the root shadows may persist for a long time. The x-ray is of especial use in cases with complications. Abscesses, localized bronchiectasis, and above all empyema may often be sharply defined when they have eluded physical examination. Especially is this so of small collections of fluid between the lobes, or along the mediastinum.

BRONCHOSCOPY.—When the presence of a foreign body is suspected, especially in a child, bronchoscopic examination may be advisable. It should be made only by an expert in bronchoscopic technic.

VITAL CAPACITY.—Study of the vital capacity is useful in indicating the degree of respiratory embarrassment and is a good index of progress in the case. A simple spirometer may be used, measurement being recorded of the volume of a forced expiration following a full inspiration.

Diagnosis.—There is no diagnostic syndrome specific of bronchopneumonia. The physician must be familiar with the conditions under which the disease is likely to occur and be on the watch. In any patient with bronchitis, acute or chronic, with any pulmonary disease such as tumor or cyst, in any acute infection especially measles, influenza, scarlet fever, diphtheria, small-pox, or sepsis, in any chronic or wasting disease, in any old debilitated or bed-ridden patient, the possibility of bronchopneumonia is ever present. It may develop insidiously without revealing symptoms or signs, but careful note of cough and sputum, and painstaking physical examination of the chest will usually save the physician from mistake. Acute severe cases are usually obvious at least in so far as the presence of an acute respiratory infection is concerned.

SPUTUM CULTURE.—The sputum culture is of the greatest importance if an exact diagnosis is to be made. The specimen should be freshly expectorated and should come from the lung and not be hawked back from the nasopharynx. After immediate macroscopic examination the specimen is washed in several changes of sterile salt solution or nutrient broth to remove contaminating bacteria from the mouth and a bit is then smeared with a sterile bent glass rod over the surface of blood agar and oleate hemoglobin agar (Avery) plates. Very often a pure culture of streptococcus, pneumococcus, influenza bacillus or other organism will be obtained. By this method one gets a good idea, if not of the original exciting cause, at least of the organisms which are perpetuating the infection. In certain cases yeasts and molds, and anaërobic organisms may be looked for by special methods if the case presents unusual features. Finally x-ray examinations may be made (*v. supra*).

Complications and Sequelae.—Bronchopneumonia is rather a complication or sequel of some other condition than itself a cause of complications or a producer of sequels. Of major importance in this connection, however, is the tendency of one attack of bronchopneumonia to be followed by others. This is so especially in cases in which there is permanent damage in the form of chronic bronchitis and emphysema, or diffuse bronchiectasis. Some patients of this sort are the unhappy subjects of regular exacerbations usually becoming more intractable on successive occasions. The lungs may finally be the seat of extensive indurative changes with damaged and dilated bronchi, the right heart becomes dilated and hypertrophied and not infrequently the final picture is one of grave cardiac failure. In other less severe cases a localized bronchitis may persist for years, especially at a base, with occasional spells of fever, cough, and expectoration and exaggeration of the pulmonary signs. Such cases are now often spoken of as subacute or chronic nontuberculous basal infections.

Among the more immediate complications of an acute attack may be mentioned empyema and abscess. They will be discussed below together with treatment. An occasional grave outcome is the development of a general septicemia.

Another complication which should be mentioned is the rare occurrence of subcutaneous emphysema. This comes about through rupture of small areas of pneumonia with leakage of air into the mediastinal tissues whence it travels to the root of the neck, there to become manifest by swelling and downy crepitation. Such emphysema occurs most often in very sick patients but in itself is not of specially serious import.

As a rule, however, acute bronchopneumonia, if not immediately fatal, is followed by complete recovery with presumable healing of the lung.

Treatment.—General Prophylaxis.—Bronchopneumonia unfortunately is not a condition which gives promise of total eradication by public health measures. As long as bacteria exists in the upper air passages and as long as the body is subject to injuries and to infection, bronchopneumonia will continue to be an important element in the termination of life.

Certain types, however, will be prevented in an indirect way by elimination of the diseases which they are prone to follow. Were measles, influenza, common colds, scarlet fever, and other acute infectious diseases wiped out a most important and fatal group of bronchopneumonias would cease to exist.

Furthermore it may be said that general improvement of hygienic conditions and education of the people along the lines of personal hygiene would be of inestimable value from the preventive standpoint. Many cases of recurring bronchopneumonia in adults are the direct consequence of a bronchitis needlessly acquired in childhood through neglect of elementary hygienic principles.

The assembling of large groups of individuals in close contact, as we learned during the World War, promotes conditions favorable for epidemics of respiratory disease which are probably largely preventable by proper measures in connection with housing and segregation.

In a more specific way general prophylactic measures may occasionally be usefully applied. In one of the military camps for example, when streptococcus bronchopneumonia following measles was epidemic, it was found that isolation of streptococcus carriers on entry to the camp cut down the incidence of complications from 36.8 per cent to 6.4 per cent. (Levy and Alexander.)

Individual Prophylaxis.—Much may be done by **special care** to prevent the development of bronchopneumonia in individual instances. In all cases of acute infectious disease, especially in the exanthemata and in influenza, the greatest care should be exercised in this regard. The patient should be **brought early to bed** and kept there until safely convalescent. It was notable in the recent influenza pandemic that those who fought the disease and carried on developed bronchopneumonia more frequently and in more severe form than those who gave up promptly and went to bed. **Good general nursing** with especial emphasis on the **hygiene of the mouth** will in the long run prevent pulmonary complications in many cases of acute infectious disease. The same may be said of the intercurrent bronchopneumonias of chronic disease.

Great care should be exercised in the administration of anesthetics. Under no circumstances should a patient take ether during the course of a cold or other respiratory tract infection, even if mild, except in cases of grave emergency, and people with chronic pulmonary disease, such as bronchitis, should safeguard themselves from exposure to cold or inclement weather and in general should avoid physical and mental overstrain.

Vaccines.—A good deal of discussion has arisen lately as to the value of vaccines in the prevention of respiratory infection. The prospect of effective prophylactic vaccination against fixed type pneumococcus lobar pneumonia is good according to the work of Blake and Cecil. But the organisms concerned in bronchopneumonia are too varied and their exact etiological status too indefinite to justify as yet the indiscriminate use of "mixed" vaccines. They are to be decried in every sense. However, in instances of chronic pulmonary infection with recurring attacks of bronchopneumonia, autogenous vaccines prepared from freshly isolated cultures of the predominating bacteria may at least be tried with a certain amount of reason. Such therapy should be carried out only by someone specially trained in biological therapy and brilliant results should not be expected.

General Treatment.—The treatment of bronchopneumonia naturally includes that of the underlying or associated condition usually present. Naturally such treatment will vary widely but as regards the pulmonary features themselves certain definite principles must be followed.

Observations.—The importance in the therapy of acute infectious diseases of **accurate observations of temperature, pulse and respiration** is so essential that this subject must properly be included under the head of treatment. Only too often a few random observations jotted down from time to time are the only records available. In the author's opinion it is quite impossible to follow intelligently the course of a febrile reaction without a careful graphic chart, which shows at a glance the character of the temperature curve, the trend of the fever, the pulse rate and its relation to the thermal reaction, and the respiratory rate. In pneumonia especially, complications such as empyema and sepsis are often first suspected by the form of the fever curve or by alterations in the heart rate which would not be significantly manifest without a graphic chart. The temperature should be recorded at least at four-hour intervals. It is preferably taken per rectum since in bronchopneumonia with dyspnea it is especially difficult for an ill patient to hold the thermometer properly in the mouth. Change from mouth to rectal temperature observations frequently reveals the presence of a degree of fever quite unsuspected. The pulse and respiratory rate should be recorded at the time as the temperature and in hospitals other useful data may be conveniently placed on the chart.

Regulation of the Patient's Activity.—Physicians have always been impressed by the importance of rest in the handling of infectious disease. Few stop, however, to consider the special rationale of rest in particular cases. In typhoid fever, for example, the patient has to face weeks of wearing infection; hence it is easy to see that his strength must be husbanded in every way. In pulmonary tuberculosis we have an additional indication in the relative immobilization of the lung which is affected by absolute quiet. There is no disease, however, in which **total physical relaxation** is more entirely essential than in pneumonia whether lobar or bronchial. It may be set down as axiomatic that pneumonia patients who are up and about, or who are moved and disturbed do badly. Hospital statistics show beyond peradventure that the outcome varies almost directly with the day of the disease on which the patient takes to bed. This was clearly brought out during the recent pandemic of influenza. In certain civil groups where early hospitalization before the onset of pneumonia was practiced the mortality was relatively low (15 per cent. in the Johns Hopkins Hospital), whereas in some of the Army Camps where the men carried on until they dropped, the distressing mortality of 45 per cent. obtained. The observation may be made daily at the bedside that even turning an ill pneumonia patient may send the respiratory rate up to 60 or 80 per minute with considerable subjective discomfort. The author has seen patients, who walked into the hospital apparently in fair condition, collapse and die as they were being put into bed. One may say, therefore, without any reservation or exception that the most fundamental point in the treatment of bronchopneumonia is to **get the patient immediately to bed.**

Once at rest the usual sick room precautions should be observed. The bed should preferably be single and should have a firm mattress which will not assume the form of a hammock under the patient's weight. Whatever position is most comfortable should be encouraged. If the patient breathes better when sitting up he should be supported by some form of back rest or by pillows suitably grouped. Restless or delirious cases must be safeguarded from injury by supports at the bedside or if necessary by some form of restraining sheet, although the latter is undesirable.

The patient should be disturbed as little as possible. Only the essential nursing procedures and examinations by the physicians should be carried out. Under no conditions should he be allowed to get out of bed.

The **bed-pan** and **urinal** must be used; if necessary the movements may be passed into a drawsheet. Pneumonia patients should not be allowed to feed themselves nor to make a single movement which can be done for them by the attendants.

Nursing Care.—If in any way possible, the patient should be under the care of a trained nurse. In severe cases he is helpless and needs an available aiding hand in the very worst way. His comfort and perhaps his life depend upon the details of care. The **daily bath** must be given with skill and with dispatch, the mouth and lips must be kept clean and fresh. The strain of coughing and expectorating is eased by competent assistance, and **water** should be offered before the patient has to ask for it. In brief the care of an intelligent and competent nurse is essential if the best results are to be obtained. The physician can for the most part do little apart from keeping up a vigilant watch for complications.

Fresh Air.—The older physicians were keen to realize that patients with lobar pneumonia did better with plenty of fresh air. Often this idea was carried to extremes, the sick one being placed out-doors perhaps in cold or inclement weather. With bronchopneumonia, however, **care** and **conservatism** must be exercised **in regulating the temperature** and **ventilation** of the sick room. Many of the patients are old and debilitated and react to cold fresh air not with a favorable response but with cyanosis and collapse. In the author's experience a **room temperature** of from **60° to 70° F. (15.5° to 21.1° C.)** with free circulation of fresh air but without exposure to draught is desirable. Under no condition should acute bronchopneumonia patients be subjected to the rigors of out-doors in winter.

Recently the use of oxygen in certain types of cyanotic cases has been considerbaly discussed. It seems clear, however, that special apparatus is necessary for the efficient use of this measure and until the procedure has been further developed it is perhaps wiser not to disturb the patient with the old-fashioned methods of inhalation which have been shown to be inefficient.

Diet.—The old saying "stuff a cold and starve a fever" can no longer be considered valid. Physiologists and physicians have shown beyond doubt not only that **liberal feeding** is desirable but also that it is feasible. In fact the introduction into the management of typhoid fever of the so-called high calory diet whereby the patient is guarded from the usual wasting with which we were all familiar even as recently as fifteen years ago has entirely modified the picture of the disease. We now know that the emaciation, delirium, carphologia, distention, sordes, etc., prominent in the older descriptions, are not essential features of typhoid fever but merely the results of neglect and underfeeding. Theoretically then a liberal ration of food would seem indicated in such infections as the bronchopneumonias. The physician's enthusiasm must be tempered, however, by one consideration, namely, the patient's reaction to the effort of ingesting large amounts of nutriments, but it is wiser to wait until the severity of the reaction has abated. Better to have the patient lose a few pounds than to jeopardize his life by overexertion. Here again the services of a skilled nurse who can sense the correct point to which feeding can be pushed are invaluable.

In a general way, however, certain directions may be laid down. The diet should approximate in caloric content as nearly as possible the maintenance requirements, roughly speaking, from 2,000 to 3,000 calories per diem for the adult of average weight. It should be offered to the patient in several—five or six—small portions rather than in the form of three larger meals, to avoid the overstrain associated with a sudden loading of the stomach. The food should be bland, mechanically non-irritating, and readily digestible, and should be of a sort which minimizes the effort of chewing. Such articles as milk, milk products, soft eggs, jellies, junkets, custards, broth, coffee, scraped meat, purée of vegetables and fruit juices may readily be combined according to the above outline. This, of course, applies to the sicker patients. In mild bronchopneumonia the feeding may be essentially similar to that in health provided intelligent conservatism is exercised.

Fluids.—One is accustomed to think of the febrile patient as craving fluids, and to be sure, the request for water is a frequent one in such cases. As a rule, however, only a few sips are taken at a time and the total voluntary intake in twenty-four hours may be considerably below normal. For this reason it is necessary to force fluids during the course of a fever. There are several manifest beneficial effects: the patient who takes plenty of water is usually in better general condition, his mental condition is clearer, his mouth is cleaner, the urine is free and does not show the usual so-called febrile characteristics—dark color, high specific gravity, albumin and casts—which are really the indication of renal irritation associated with the excretion of an overconcentrated urine. The question naturally comes up then as to the optimum amount of fluid to be ingested. Forcing of fluids may readily be pushed to an extreme. It should be remembered that an intake of over 5 liters (10.57 pints) per day means almost constant exertion in the form of drinking and of voiding, and such effort is an important consideration in the case of bronchopneumonia patients. In the author's experience an **intake** of from **2** to **4 liters of fluid daily** produces an optimum result without undue burden. In totally uncoöperative, delirious or comatose patients **rectal infusions** of water or **subcutaneous** infusions of physiological salt solution should be given.

Care of Bowels.—Here again the question of sparing the patient is paramount. One or two easy movements a day are desirable. An **enema** should usually be given to empty the lower bowel and thereafter the choice of cathartic is a matter of experiment to suit the individual case. **Moderate purgation** with **calomel, grains** ii (0.13 gram), in the evening, followed by ½ to **1 ounce (15.55 to 31.10 grams)** of **epsom salts** on the following morning, usually produces the desired result. In some cases mild laxatives such as **cascara, phenolphthalein, and rhubarb and senna** may be adequate. Diarrhea is infrequent but distention is common. The latter if extreme indicates a severe type of disease and in the author's experience is usually not amenable to local treatment. As the general condition improves the bowel regains its tone and distention subsides. Enemas, stupes, and injections of pituitrin may be tried but usually they produce no striking effects.

Hydrotherapy.—Except in the case of desperately ill or moribund patients a **daily** cleansing **bed bath** should be given. Sponges and tubs for therapeutic purposes are undesirable in bronchopneumonia. The patients usually react badly and if at all debilitated may collapse following the treatment.

Drugs.—There are no drugs which have any specific effect on the bronchopneumonic process itself save in the occasional case where the underlying disease can be attacked. The use of drugs is therefore more properly taken up under symptomatic treatment.

Symptomatic Treatment.—*Pleural Pain.*—In many cases of bronchopneumonia extension of the inflammatory process to the surface of the lung may set up a pleurisy with the usual syndrome of distressing pain in the side or upper abdomen with accentuation on respiration. For relief of this symptom the administration of **morphia** is of paramount importance. It should be given promptly in doses (in adults) of from **1-6 to 1-4 grain (0.0108 to 0.0162 gram)**, repeated if necessary every four to six hours. No substitute, such as codein, can effectively take its place, nor is there any contraindication to its use except in old or extremely debilitated individuals, who already show evidence of embarrassment of the respiratory center. In such cases the dose should be small and its effect should be carefully watched.

Local measures in the author's experience have proved cumbersome and usually unsatisfactory. Poultices, for example, are difficult to prepare well, and are hot and messy. Strapping with adhesive plaster gives no relief unless done with the greatest exactness; it has the disadvantage of irritating the skin and for the time being rendering physical examination unsatisfactory. Occasionally a **light ice-bag** applied intermittently over the painful area may give some relief.

Cough.—A great deal may be said about the management of cough, —one of the most distressing symptoms in bronchopneumonia. It should be remembered that cough may arise from irritation in the air passages, even though little sputum is present, or that it may be stimulated by the presence of exudate in the bronchi. In the former case the cough is useless and incommodes the patient in the most disagreeable sort of way. It is highly desirable therefore to check such cough and this is best done by **general sedatives. Morphia** again is of the greatest value though **heroin,** owing to its special action on the respiratory center, is also useful. **Heroin** and **codein** together form a very effective combination (**codein sulphate, ½ grain [0.0324 gram], heroin hydrochlorid, 1-12 grain [0.0054 gram]**). **Inhalations** may give relief although some patients respond to them with increased cough. The simplest form of procedure in the case of the adult is to place the drug in the bottom of a pitcher or large glass flask and then to pour in boiling water. The patient inhales the medicated fumes under the shelter of a blanket thrown over his head. Care should be taken to avoid exposure to draught after such an inhalation. It may be repeated at intervals of a few hours if it gives relief. As a base for the inhalation the following preparations have been found satisfactory:

℞
Menthol, ʒi (3.9 grams).
Alcohol, f℥iiss (74.20 c.c.).
Sig.: fʒi (3.75 c.c.) to pint of hot water as inhalation.

or

℞
Creosote
Tincture benzoin compound
Turpentine, āā fʒii (7.5 c.c.).
Sig.: fʒi (3.75 c.c.) to quart of hot water as inhalation.

In the case in which the cough is productive of large amounts of sputum much discrimination is necessary. While it is desirable to relieve the patient of the strain of coughing, it is equally important that the exudate in the bronchi should be brought up. Injudicious use of sedatives in such cases may lead to retention of secretions, respiratory embarrassment and, perhaps, an unfavorable outcome. The author has found it a satisfactory procedure to attempt to empty the bronchi as completely as possible in the morning and evening and then to give sedatives. In this way the patient, as it were, concentrates most of his coughing into several short periods with relative freedom in the interval. Such drainage may be accomplished by urging the patient voluntarily to cough, by giving a stimulating inhalation, or by posture. Unless the patient's general condition contraindicates, the latter is worth a trial. By means of some sort of device the patient is put in the head-down position at an angle of about 45 degrees. He may bend over the back of a chair, or be placed in a wheel-chair, or tilted by means of a specially devised invertible chair into which he is strapped. As a rule there is free cough with abundant drainage of sputum if the procedure is continued for from five to fifteen minutes. Garvin and others have found this method especially useful in the cases associated with bronchiectatic cavities.

In cases of bronchopneumonia in which an asthmatic element is prominent, urgent measures are indicated. If the breathing becomes very labored and if cyanosis is marked, the patient should be placed in a **steam tent. Adrenalin hypodermically (15 ♏** [1-1000]), or **atropin,** grain 1/100 to 1/50 (gram 0.00065 to 0.0013) may be given. Other drugs such as ammonium chlorid and tartar emetic have in the author's experience produced no definite result, although **potassium iodid** in small doses, grains 5 to 10 (gram 0.234 to 0.65), may aid in loosening the secretions.

Dyspnea.—As an isolated symptom dyspnea is best relieved by **morphin.**

Restlessness, Insomnia and Apprehension.—The treatment of these symptoms as such is essentially a problem of sedatives. Morphin, except in so far as it eliminates positive discomfort, excites rather than quiets.

Veronal, chloral hydrate, bromids, and **codein** are especially useful, and their individual effect is enhanced by combinations such as **veronal, grains 5 to 10** (gram 0.324 to 0.65), with **codein sulphate,** grain ½ to 1 (gram 0.0324 to 0.065), or **chloral hydrate, grains 10 to 15** (gram 0.65 to 0.972), with **sodium bromid, grains 30 to 60** (grams 1.95. to 3.9).

Delirium.—Delirium is a symptom both alarming and difficult to manage. Its onset usually indicates a turn for the worse with profound intoxication or collapse. From the standpoint of drugs, **amylene hydrate** or **paraldehyd** by mouth in dram (3.75 c.c.) doses, or **hyoscin** hypodermically, grain 1/200 to 1/75 (gram .000325 to 0.00389) are useful. In those cases in which previous use of alcohol may have been a factor in producing delirium, **whisky** should be given. Restraint must of course be used in a judicious way, recognizing that the patient's struggles against a straining jacket are if possible to be avoided.

Circulatory Failure.—Circulatory failure is the symptom which medical tradition has marked as the most alarming and difficult to manage in pneumonia, and on the appearance of rapid pulse with low blood-pressure the physician has usually instituted the administration of stimulants such as **strychnia, caffein, camphor,** and **ergot.** Gibson's index —the ratio of the pulse in beats per minute to the systolic blood-pressure in millimeters of mercury—may be recalled. When this ratio became greater than unity it was regarded as a danger signal of circulatory failure and an indication for the use of emergency measures. Questioning the validity of Gibson's idea, Newburg and Minot studied the blood-pressure in a series of pneumonia cases and brought out the fact that the systolic pressure was higher in those who died than in those who recovered. Newburg also showed that the vasomotor reflexes were not abolished in pneumonia by stimulating the cut sciatic nerve in animals moribund from pneumococcus sepsis obtaining rises in blood-pressure of as much as 45 per cent. Furthermore, Newburg and Porter showed that the heart in experimental pneumonia contracted normally when perfused with normal blood but showed signs of insufficiency when perfused with blood from an animal with severe pneumonia, although if the latter were fed gradually the heart could largely adjust itself.

As a matter of fact clinical study also shows that cardiac failure as an isolated event occurs only very rarely in pneumonia. Any evidences of insufficient circulation are usually bound up with those of a generalized terminal collapse. Not only the heart but the entire organism fails and one sees the familiar picture featured by collapse, coma, cyanosis, respiratory failure, edema of the lungs, abdominal distention, and rapid feeble pulse. This state of affairs is usually associated with a terminal septicemia and indicates an entire collapse of the reactive processes in the body and speedy death. The treatment in these cases is, in the author's experience, invariably futile although by vigorous stimulation the duration of life may be extended by a few hours. **Strophanthin,** milligram 1 (.0154 grain), may be injected instramuscularly or intravenously; **caffein sodium benzoate,** grains 3 (0.195 gram); or **atropin,** grain 1/50 (0.00130 gram) hypodermically; or **adrenalin,** minims 15 to 30 (0.92 to

1.90 c.c.). The **foot of the bed** should be **elevated,** and **a subcutaneous infusion of salt solution,** 1 to 2 liters (2.1135 to 4.227 pints) may be given.

But apart from circulatory failure of this sort, cardiac failure in the usual sense may occasionally occur as an isolated event in a patient otherwise not in desperate straits. This accident is confined to those individuals with antecedent cardiac disease who are subject to heart failure under stress or strain of any sort. Where there is an old valve lesion, or myocardial disease, insufficiency with the usual picture of congestive heart failure—edema, cyanosis, orthopnea, and engorgement of the viscera—may supervene. In the case of bronchopneumonia this is seen more especially in old cases of chronic bronchitis and emphysema with dilatation and weakening of the right heart or in old individuals with arteriosclerosis and senile myocardial changes. In these cases the treatment is that of myocardial insufficiency from any cause—limitation of diet, of fluids, and of salt, digitalis and the caffein diuretics, and in instances associated with acute cardiac dilatation and edema of the lungs, venesection.

There has been a great deal of discussion in the literature recently following the work of Cohn as to the advisability of **digitalizing** pneumonia patients at the start with a view of preventing possible later disturbances of mechanism such as auricular fibrillation and flutter which may occasionally supervene during the course of a pneumonia. There is certainly no objection to such a procedure provided the drug is not pushed to the point of producing toxic symptoms—nausea, vomiting and extrasystoles. In the average adult from **18 to 24 c.c.** of a **standardized tincture** (1 c.c.=1 cat unit) may be safely given in **3 to 6 doses** over a period of one to two days. **The author's experience has not impressed him with the usefulness of routine digitalization of pneumonia patients.**

SPECIFIC THERAPY.—The subject of specific therapy may be discussed in a few words. In cases of bronchopneumonia following diphtheria, antitoxin should, of course, be given promptly and intensively, and in the occasional instance due to infection with Type I Pneumococcus the specific serum developed at the Rockefeller Institute should be employed. Vaccines in acute bronchopneumonia are, the author believes, at present entirely useless; in fact they may do harm if a severe reaction follows. In recurring cases associated with chronic bronchitis or bronchiectasis, autogenous vaccines made from the organisms predominating in the sputum may be administered in the hope of improving the general pulmonary condition although such procedures have in the author's experience been disappointing. Stock vaccines of miscellaneous bacteria offer no reasonable appeal in conscientious therapy. In any case the vaccine should always be used by one experienced in bacteriology and vaccine therapy if deleterious results are to be avoided.

ISOLATION.—Inasmuch as bronchopneumonia is often due to highly virulent bacteria which may be readily transmitted from person to person, measures should be used to protect the attendants and others from danger of infection. The organism may be disseminated by cough or more indirectly by contamination with sputum of the attendant's hands or of objects in the sick room.

The patient is preferably placed in a room by himself. In hospitals, if this is not practicable, screens or sheets should be hung between the beds. The patient should be instructed to cover his mouth whenever possible on coughing, and to be careful to expectorate into a closed receptacle. Paper or cardboard sputum cups are best since they can be burnt together with their contents. All dishes and utensils should be boiled after using and linen should be disinfected or boiled. The attendants should be limited in number and the members of the general household should not be indiscriminately allowed in the sick room.

Those in immediate contact with the patient should wear a gown and a gauze face mask which may be removed on leaving the room. The attendant's hands should be carefully scrubbed with soap and water and then soaked in a 1/1000 bichlorid solution for several minutes after handling the patient or the discharges.

Treatment of Complications.—In as much as bronchopneumonia is a disease of such protean manifestation and associations its complications are in a sense limitless. The present discussion therefore will be confined to those complications and sequelæ which are directly related to the pulmonary process.

Empyema.—As in lobar pneumonia empyema is a frequent and important complication. Figures as to incidence cannot be presented in a satisfactory way because its occurrence varies in different types of bronchopneumonia. In the acute cases following the exanthemata it is especially likely to supervene, and in the postinfluenzal bronchopneumonias the incident of purulent pleurisy was especially high. One must be on the lookout for empyema from the onset. The early thin effusions loaded with bacteria are the precursors of a fatal generalized sepsis unless promptly dealt with. At this stage of the disease the diagnosis is made by physical signs and the examiner should search with special care for the evidence of a beginning collection of fluid at a base. Such effusion may pour out with amazing rapidity; the author has frequently discovered evidences of a large pleural effusion within twelve hours after a negative examination. Any reasonable suspicion of empyema should be confirmed if possible by roentgenogram or by exploratory aspiration.

There has been much discussion in the literature as to when and how to deal with these early empyemas. Some advise waiting with the idea that early interference may promote a sepsis whereas the fluid if allowed to localize may later be evacuated with safety. The final decision must, of course, be left to the surgeon—and preferably to one skilled in thoracic work—who will base his action on the special features of the case. It has been the author's practice, however, on the fundamental principle that pus under tension leads to grave danger of sepsis, to **drain all cases of empyema as soon as the diagnosis is made.** In some cases it has been necessary owing to the poor condition of the patient to make a simple intercostal incision in the ward and to insert a small tube instead of doing a more radical rib resection, and the results have justified the feeling that if reasonably competent surgical assistance is available early drainage is always advisable.

In another group of cases empyema occurs late or, indeed, does not become manifest until the pneumonic process itself is presumably healed. Empyema under these conditions, unfortunately for the diagnostician, does not usually unmask itself by presenting frank signs of pleural fluid. Collections of pus may become localized in the costophrenic angles, along the mediastinum or between the pulmonary lobes. Persistent malaise, secondary rise of temperature or failure of the curve to become entirely normal and leukocytosis are perhaps the most important clues which arouse one's suspicion. They call for frequent and scrupulous physical examinations, bearing in mind that a patch of incompletely resolved pneumonia or of atelectatic lung may be most deceptive. However, a persistent area of impairment or of flatness with suppression of breath sounds or hollow tubular breathing justifies the exploratory needle and if possible roentgenographic study. Stereoscopic x-ray plates are especially useful in localizing interlobar empyema. When the diagonsis is made, surgical drainage should be done with all possible speed, although interference is not as urgent as in the acute purulent pleurisies.

Abscess.—Abscess occasionally follows bronchopneumonia. A variable period of latency lasting days, weeks or even months may elapse although there is rarely complete restoration of health in the interval. The symptoms in mildest form include malaise of slight degree while in severe cases prostration, chills, fever, sweats, progressive weakness and anemia, with persistent cough and expectoration occur. The physical signs are usually disappointing. In the occasional case there may be frank signs of cavitation with dulness or an amphoric note, amphoric or tubular breathing and coarse râles, but as a rule a patch of râles with slight impairment is all that is made out. Variability of signs from day to day is characteristic and at times careful physical examination may reveal no definite abnormality in the lungs. Such findings are readily intelligible when one remembers that pulmonary abscess, save in old long-standing cases with great destruction of tissue and peripheral fibrosis, usually consists of an area of necrosis riddled with small cavities which under variable conditions of drainage will naturally present different signs. Diagnosis must be made from (1) the general septic symptoms and (2) the sputum. The latter may be mucopurulent but more often is characteristically foul and microscopically may show the evidences of pulmonary disintegration in the form of elastic tissue fibres. It varies in amount from time to time—occasionally there may be sudden profuse expectoration which suggest the emptying of retained secretions. Roentgenograms are of great value in exact localization although the conservative roentgenologist may often hesitate without knowing the clinical features in the differentiation of abscess, bronchopneumonia or thickened pleura.

Pulmonary abscess occasionally heals spontaneously under rest and general measures but this is the exception. The physician is on the horns of the dilemna. Operation is unsatisfactory in late cases where a rigid fibrous wall has developed about the cavity and usually results in a fistula which cannot be closed. On the other hand early operation is dangerous and means superfluous interference in a case which would have healed spontaneously. At any rate operation should be done only by an expert in thoracic surgery. Unless such a man is available it may be wiser to employ rest and general upbuilding measures.

CONVALESCENCE.—Conservatism should be the key-note in the management of convalescence. All patients with bronchopneumonia should be kept in bed until the temperature has been normal for at least ten days to two weeks, depending upon the severity of the case, and until the patient feels perfectly well. If possible this period of rigid control should be extended until cough and sputum have entirely disappeared and until the lung is clear on physical examination. Too much stress need not be placed on the persistence of a few râles or areas of impure breath sounds provided the constitutional reaction has entirely subsided, the leukocyte count is normal, and the nutrition and well-being good. The physician should be sure that no complication such as empyema or abscess has developed insidiously and not been recognized. He should remember that in acute cases occurring in previously undamaged lung no conservatism is too extreme if complete healing can be achieved and the patient thereby safeguarded against recurrent attacks which will lead to permanent lung damage and eventual disaster.

As in convalescence from any acute infection increase of activity should be very gradual at first and attempt at systematic upbuilding by liberal diet, fresh air and protection from strain should be carried out. All predisposing factors to subsequent attacks should be avoided—exposure to inclement weather, irritating gases, etc.

Prognosis.—Prognosis in bronchopneumonia depends upon a number of factors all of which must receive consideration.

AGE.—Other things being equal the outlook is less favorable in infants and very old people who are more susceptible to respiratory infection than healthy young adults.

PATIENT'S GENERAL CONDITION.—This is of great importance. Bronchopneumonia coming on in bed-ridden, debilitated or cachectic individuals is notably grave and often fatal in its outcome.

CONSIDERATIONS OF PREDISPOSING DISEASE.—Bronchopneumonias occurring as complications during the course of epidemics of infectious disease, such as measles or influenza, are likely to be more serious than those occurring in nonepidemic times. The fulminating postinfluenzal pneumonias of the military camps are instances of this sort.

Cases which are put under treatment early and receive good general care are much more favorable than those which run their course neglected and in poor hygienic surroundings.

Pathology.—The gross appearance of the uncut lung may show little abnormal in cases where the process is of slight extent and deep seated, but usually there are visible on the surface especially in the lower lobes small areas which may project slightly and be of a different shade from the surrounding lung tissue. On palpation these nodules are appreciable as finer noncrepitant areas in the surrounding air-containing tissue. On section the areas of solidification stand out as slighly elevated dark patches. The intervening lung may be relatively normal and air-containing or edematous or atelectatic. There is great variation in the extent of the process which may consist of only a few small scattered patches or of large confluent areas which in the gross closely simulate a lobar pneumonia. The smaller bronchi show evidences of inflammation and usually contain pus and it may be possible to demonstrate the relationship of such a bronchiole to a surrounding patch of consolidation. The pleura may be normal—usually there is some loss of luster over patches of pneumonia which have reached the pleural surface, or an outspoken fibrinous pleurisy may be present. In other cases actual collections of pus are found.

The above description applies to the average case of terminal or intercurrent bronchopneumonia. The picture may be modified by special conditions such as the presence of a foreign body, or preëxisting pulmonary diseases.

Microscopically the alveoli in the affected areas contain inflammatory products, especially leukocytes and epithelial cells. In contrast to lobar pneumonia fibrin is usually not present nor are there large numbers of red cells. The walls of the air cells are swollen, the capillaries are congested and leukocytic infiltration in the interstitial tissues is present. The bronchi are distended with pus and their walls show infiltration with inflammatory cells.

The pathological anatomy of special types of bronchopneumonia has recently been studied with special care. MacCallum and others have pointed out in the case of the postinfluenzal and postmeasles bronchopneumonias that a great variety of types of reaction may be encountered depending apparently upon the intensity of the epidemic and the kinds of bacteria involved. MacCallum divides the cases into the following:

(1) Interstitial bronchopneumonia.
(2) Interstitial bronchopneumonia with lobular pneumonia.
(3) Lobar pneumonia with interstitial bronchopneumonia.

He describes the changes in the interstitial bronchopneumonia as follows: "The typical change in the pleura consists in the effusion of a large quantity of thin turbid fluid into the pleural cavitiy. This is usually brownish with a fine granular sediment which is stirred up on moving the lung, but there are generally also floating shreds of fibrin. The surface of the pleural membranes is covered with fibrin under which hemorrhages are often visible. There are cases in which, although the lungs are diffusely affected, the pleural surfaces are perfectly smooth and the cavity is practically dry. There are various later modifications of the character and distribution of the effusion leading to its encapsulation and to a more definitely purulent character which forms the rule in cases which survive long enough.

"The essential features in the gross appearance of the lungs in interstitial bronchopneumonia lie in the filling of the bronchioles with opaque exudate, the thickening of their walls, and the consolidation of the adjacent lung tissue which appears in cross section as a nodule and in longitudal section as a hardened mantle of dense tissue bordered with hemorrhage accompanying the bronchiole. Atelectasis of the intervening lung substance, great thickening and prominence of the interlobular septa and pleura, and usually pleurisy with abundant effusion make up the whole picture. The bronchial glands are somewhat enlarged and soft. The mucosa of the large bronchi is deeply reddened and covered with purulent exudate and sometimes with a necrotic pseudomembrane."

Histologically the essential change is an interstitial inflammation. "In all the later stages this change in the connective tissue, elastic tissue, and musculature which make up the wall of the bronchus is striking. The normal elements are spread apart by great numbers of mononuclear cells which intercalate themselves between the fibers and often form a mass which lifts up and dislodges the epithelium. In some cases the bronchi become dilated to a marked degree. In the most advanced condition the walls of the bronchioles become enormously thickened and form a compact tube of infiltrated tissue." The exact type of reaction in the alveoli is variable depending upon the stage and severity of the disease.

In the cases in which the "lobular" type of bronchopneumonia occurs "the gross appearance is usually different from that found in interstitial bronchopneumonia, since these areas of consolidation are no longer nodular, hard, and prominent, nor especially situated about the branches of the bronchi. Instead they are very rough, grey, and slightly elevated, often confluent in quite large patches where they closely resemble in texture the consolidation of pneumococcal lobar pneumonia. The participation of the lymphatics is extremely striking, great beaded canals distended with opaque yellow pus so as to become very conspicuous accompany the blood-vessels and bronchi or run in the line of the interlobular septa to the pleural surface."

In the fulminating postinfluenzal streptococcus pneumonias still another type of reaction was seen which was featured by intense hemorrhagic edema of the lung with little local exudate but profound necrosis of the tissues. Cases associated with the presence of staphylococcus aureus on the other hand tended to exhibit local small abscess formation.

This brief outline indicates the great variability in the detail of the pathology of bronchopneumonia which appears to be related, as pointed out above, to the nature and severity of the predisposing infection, to the virulence of the secondarily invading organisms and to their variety and upon the route of invasion (bronchial, hematogenous, lymphatic).

Aside from the lung changes the pathological findings are those of any acute infection—cloudy swelling of the viscera, acute splenic tumor, etc. In addition a great variety of conditions produced by antecedent or associated disease may occur.

BIBLIOGRAPHY

General Texts

Fraenkel, A. Spezielle Pathologie und Therapie Der Lungenkrankheiten, Berlin and Wien, Urban & Schwarzenberg, Berlin, 1904.

Hamman, L. Diseases of the lungs. Oxford Medicine, Oxford University Press, 1920, II, 49.

Lord, F. T. Disease of the bronchi, lungs and pleura. Lea & Febiger, Philadelphia, 1915.

Etiology

Blake, F. G., and Cecil, R. L. Production of an acute respiratory disease by inoculation with bacillus influenzæ. Jour. Amer. Med. Assoc., 1920, lxxiv, 170.

Bloomfield, A. L. The mechanism of elimination of bacteria from the respiratory tract. Amer. Jour. Med. Sc., 1922, clxiv, p. 854.

Chickering, H. T., and Park, J. H. Staphylococcus aureus pneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 617.

Elwyn, H. Postoperative pneumonia. Jour. Amer. Med. Assoc., 1922, lxxix, p. 2154.

Glover, J. A. Six cases of purulent bronchopneumonia associated with the meningococcus. Lancet, 1918, ii, 880.

Goldbloom, A. Bronchopneumonia following aspiration of zinc stearate powder. Canad. Med. Assoc. Jour., 1922, xii, 491.

Kinsella, R. A. The bacteriology of epidemic influenza and pneumonia. Jour. Amer. Med. Assoc. 1919, lxxii, 717.

Kline, B. S. Spirochetal pulmonary gangrene. Jour. Amer. Med. Assoc., 1921, lxxvii, 1874.

Luetscher, J. A. A bacteriological and clinical study of the non-tuberculous infections of the respiratory tract with special reference to sputum cultures as a means of diagnosis. Archives of Inter. Med., 1915, xvi, 657.

Mudd, S., Grant, S. B., and Goldman, A. Reactions of nasal cavity and postnasal space to chilling of body surface; vasomotor reactions. Jour. Exper. Med., 1921, xxxiv, 11.

Nichols, H. J., and Stimmel, C. O. Pneumobacilli as complicating organisms in influenzal pneumonia. Jour. Amer. Med. Assoc., lxxii, 1919, 174.

Olitzky, P. K., and Gates, F. L. Experimental studies of nasopharyngeal secretions from influenza patients; bacterium pneumosintes and concurrent infections. Jour. Exper. Med., 1921, xxxiv, 1.

Opie, E. L. Pneumonia following influenza. Jour. Amer. Med. Assoc., 1919, lxxii, 556.

Schade, H. Untersuchungen in der Erkältungsfrage. Münschr. med. Wchnschr., 1919, lxvi, 1021.

Winternitz, M. C., Smith, G. R., and Robinson, E. S. An unrecognized pathway for bacteria invasion of respiratory tract. Bull. Johns Hopk. Hosp., 1920, xxxi, 63.

Winternitz, M. C., Smith, G. H., and McNamara, F. P. Effect of intrabronchial insufflation of acid. Jour. Exper. Med., 1920, xxxii, 199.

Winternitz, M. C., and Lambert, R. A. Edema of lungs as cause of death. Jour. Exper. Med., 1919, xxix, 537.

Wollstein, M., and Meltzer, S. J. Jour. Exper. Med., 1912, xvi, 126.

Wollstein, M., and Meltzer, S. J. Jour. Exper. Med., 1913, xviii, p. 548.

Clinical Features

Aufrecht, E. Die Lungenentzündungen. Nothnagel, Spec. Patho. Therap., 1899, xiv, 232.

Barach, A. I., and Woodwell, M. N. Studies in oxygen therapy. II. In pneumonia and its complications. Arch. Int. Med., 1921, xxviii, 394.

Beddard, A. P., and Eyre, J. Acute lobular pneumonia and bronchopneumonia. Allbutt and Rolleston, System of Medicine, 1912, Vol. V, 174. MacMillan Co., London.

Conner, L. A. Symptomatology and complications of influenza. Jour. Amer. Med. Assoc., 1919, lxxiii, 321.

Fletcher, W. Meningococcus bronchopneumonia in influenza. Lancet, 1919, i, 104.

Galbraith, J. B. D. Bronchopneumonia with pyemic skin manifestations resembling small-pox. Brit. Med. Jour., 1921, ii, 526.

Hamman and Wolman. Tr. Nat. Assn., Study and Review of Tuberculosis, 1916, 171.

Hart, T. S. Heart in bronchopneumonia. Observations on activity of heart and its response to digitalis made during recent epidemic. Amer. Jour. Med. Sc., 1919, clviii, 649.

Jones, F. A. Bronchopneumonia in present influenza epidemic. N. Y. Med. Jour., 1918, cviii, 811.

Lenhartz, H. Die septischen Erkrankungen. Wien, 1903, A Hölder.

Lundsgaard, C. Studies of oxygen in venous blood. V. Determinations on patients with anemia. Jour. Exper. Med., 1919, xxx, 147.

Miller, J. A. Non-tuberculous pulmonary infections. Amer. Jour. Med. Sc., 1917, cliv, 805.

Riesman, D. Protracted unilateral bronchopneumonia of lobar distribution. Penna. Med. Jour., 1922, xxvi, 255.

Stadie, W. C. Oxygen of arterial and venous blood in pneumonia and its relation to cyanosis. Jour. Exper. Med., 1919, xxx, 215.

Stone, W. L., and **Swift**, G. W. Influenza and influenzal pneumonia at Fort Riley, Kansas, from Sept. 15 to Nov. 1, 1918. Jour. Amer. Med. Assoc., 1919, lxxii, 487.

Prevention

Doust, B. C., and **Lyon**, A. B. Face masks in infections of the respiratory tract. Jour. Amer. Med. Assoc., 1918, lxxi, 1216.

Haller, D. A. and **Colwell**, R. C. The protective qualities of the gauze face mask; experimental studies. Jour. Amer. Med. Assoc., 1918, lxxi, 1213.

Levy, R. L. and **Alexander**, H. F. The predisposition of streptococcus carriers to the complications of measles; results of separation of carriers from non-carriers at a base hospital. Jour. Amer. Assoc., 1918, lxx, 1827.

McCoy, G. W., **Murray**, V. B., and **Teeter**, A. L. Jour. Amer. Med. Assoc., 1918, lxxi, 1997.

Rosenow, E. C. Prophylactic inoculation against respiratory infections. Jour. Amer. Med. Assoc., 1919, lxxii, 31.

Weaver, G. H. Further experience with face masks. Jour. Amer. Med. Assoc., 1918, lxxi, 1405.

Vaughan, V. C., **Vaughan**, H. F., and **Palmer**, G. T. Epidemiology and Public Health. St. Louis, 1922, Vol. I.

Complications

Berkeley, H. K., and **Coffen**, T. H. Generalized interstitial emphysema and spontaneous pneumothorax as complications of bronchopneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 535.

Brooks, H., and **Cecil**, R. L. A study of eighty cases of empyema at Camp Upton. Archiv. of Inter. Med., 1918, xxii, 269.

Clarke, T. W., and **Marine**, D. Pulmonary gangrene following foreign bodies in the bronchi. Amer. Jour. Med. Sc., 1906, cxxxi, 505.

Cohn, A. E. The clinical pharmacology of digitalis. The action of digitalis discussed in the light of experimental data and of clinical observation as it affects the rate of ventricles, the blood-vessels and kidneys. Med. Clin. N. America, 1917, i, 563.

Lord, F. T. The diagnosis and treatment of abscess and gangrene of lungs, with special reference to operation. Inter. Clin., 1906, Vol. II, Sixteenth Series, 57.

Lynah, H. L. Bronchoscopic studies of pulmonary abscess. Jour. Amer. Med. Assoc., 1921, lxxvii, 1548.

McCrae, T. and **Funk**, E. H. Bronchiectasis of the upper lobes with report of five cases with necropsy. Jour. Amer. Med. Assoc., 1916, xlvii, 1060.

Wessler, H. Suppuration and gangrene of the lung. A study of one hundred cases. Jour. Amer. Med. Assoc., 1919, lxxiii, 1918.

Diagnosis

Barjon, F. Radio-diagnosis of pleuro-pulmonary affections. Translation by Honeij, New Haven, 1918.

Duken, J. Beitrag zur klinischen und röntgenologischen Diagnostik der Bronchoneumonia im kindesalter. München. med. Wchnschr., 1920, lxvii, 63.

Foster, N. B. Notes on the diagnosis of bronchopneumonia and its complications. Amer. Jour. Med. Sc., 1921, clxi, 1.

Treatment

Avery, O., Chickering, H. T., Cole, R. I., and Dochez, A. R. Acute lobar pneumonia, prevention and serum treatment. Monographs of the Rockefeller Insti-Institute, 1917, No. 7.

Barach, A. L. Therapeutic use of oxygen. Jour. Amer. Med. Assoc., 1922, lxxix, 693.

Cohn, A. E. Digitalis in pneumonia. Jour. Exper. Med., 1917, xxv, 65.

Garvin, A. H. Chronic non-tuberculous lung affection. Amer. Rev. of Tuber., 1917, 16.

Kahn, M. H. Serum treatment of post-influenzal bronchopneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 102.

McGuire, L. W. and Redden, W. R. Treatment of influenza pneumonia by use of convalescent human serum. Preliminary report. Jour. Amer. Med. Assoc., 1918, lxxi, 1311.

O'Malley, J. J. Treatment of influenzal pneumonia with plasma of convalescent patients. Jour. Amer. Med. Assoc., 1919, lxxii, 34.

Ross, C. W. Influenzal pneumonia. Jour. Amer. Med. Assoc., 1919, lxxi, 1992.

Stoll, H. F. Value of convalescent blood and serum in treatment of influenzal pneumonia. Jour. Amer. Med. Assoc., 1919, lxxiii, 478.

Pathology

Goodpasture, E. W. Bronchopneumonia due to hemolytic streptococci following influenza. Jour. Amer. Med. Assoc., 1919, lxxii, 724.

LeCount, E. R. Pathologic anatomy of influenzal bronchopneumonia. Jour. Amer. Med. Assoc., 1919, lxxii, 650.

MacCallum, W. G. Pathology of pneumonia following influenza. Jour. Amer. Med. Assoc., 1919, lxxii, 720.

Steinhaus, F. Histologische Untersuchungen über die Masernpneumonie. Beitr. z. Path. Anat., 1901, xxix, 524.

CHAPTER LIII

PYOGENIC INFECTIONS

By Max Minor Peet, M.A., M.D.

Introduction, p. 421.
Streptococcus septicemia, p. 422:—Definition, p. 422; Etiology, p. 422; Symptomatology, p. 426; Diagnosis, p. 428; Complications, p. 428; Association with other diseases, p. 428; Treatment, p. 429; Prognosis, p. 431; Pathology, p. 431.
Staphylococcus septicemia, p. 433:—Definition, p. 433; Etiology, p. 433; Symptomatology, p. 434; Diagnosis, p. 436; Treatment, p. 437; Prognosis, p. 438; Pathology, p. 438.
Colon bacillus septicemia, p. 439:—Etiology, p. 439; Symptomatology, p. 440; Diagnosis, p. 441; Complications and sequelae, p. 442; Treatment, p. 442; Prognosis, p. 442; Pathology, p. 442.
Bacillus pyocyaneus septicemia, p. 443:—Definition, p. 443; Etiology, p. 443; Diagnosis and symptomatology, p. 447; Complications, p. 448; Sequelae, p. 449; Association with other diseases, p. 449; Clinical varieties, p. 450; Treatment, p. 450; Prognosis, p. 451; Pathology, p. 451; Historical summary, p. 452.
Septicemia due to the bacillus mucosus capsulatus, to the micrococcus tetragenous, to the meningococcus, to the pneumococcus, and to the gonococcus, p. 452:—Bacillus mucosus capsulatus septicemia, p. 452; Micrococcus tetragenous septicemia, p. 453; Meningococcus septicemia, p. 453; Pneumococcus septicemia, p. 453; Gonococcus septicemia, p. 454.
Bibliography, p. 454.

Introduction.—Generalized pyogenic infections are included under the term septicemia. In ordinary classifications three groups are given. septicemia, pyemia and bacteriemia. By septicemia we mean those generalizing infections in which the organisms multiply in and are carried by the blood stream with the production of definite symptoms and lesions. Bacteriemia undoubtedly exists at times in many healthy individuals without an actual infection developing. The term pyemia has been used to distinguish the rather large group of generalized infections in which metastatic abscesses develop. We object to the term pyemia and to this attempt at distinction, as practically all septicemias, no matter what the organisms involved, have at times the characteristics of a pyemia. That is, during the course of the disease infected emboli are discharged, carried by the blood stream to distant parts and set up new foci of infection. Strictly speaking, then, pyemia is simply a complication of a general septicemic process. A large number of organisms have at times been found in the blood stream and symptoms apparently referable to their presence have been noted. The most common are the streptococci, staphylococci, and bacillus coli. The bacillus pyocyaneus should perhaps be included here. The more uncommon organisms producing septicemias are: bacillus mucosus capsulatus, micrococcus tetragenous, meningococcus, pneumococcus and gonococcus. Occasionally the anthrax bacillus produces a rapidly fatal septicemia. In very debilitated individuals organisms which are ordinarily purely saprophytic have been known to produce a generalized infection. Among these should be mentioned organisms of the proteus group and the bacillus subtilis. In some epidemics the influenza bacillus has been frequently reported but its exact pathogenicity has not been determined. Septicemias of various types have been recognizd from the earliest time but only with the development of modern blood culture methods has the particular offending organism been determined. Puerperal septicemia was quite clearly described by Hippocrates and the writings of Celsus frequently mention conditions which we now recognize as septicemia.

The treatment of septicemia is still in an experimental stage. Much had been hoped for from vaccines and serums when they were first introduced but the results on the whole have been quite disappointing. Possibly some of this may be due to improper methods of manufacture and now that the various technical processes are perfected and as more potent products develop we may hope that the frequent negative results which have been reported in the past will be replaced by those of a much more favorable outcome.

STREPTOCOCCUS SEPTICEMIA

Definition.—Streptococcus septicemia is a generalized streptococcus infection in which the organisms multiply in and are carried by the blood stream.

Etiology.—The predisposing causes may in a general way be divided into two groups: those which lower the individual resistance to infection, and those which offer an especially favorable portal of entry. Extremes of temperature, whether high or low, are not important etiological factors but may act as contributing agents through their influence on body resistance. Sudden marked fluctuations in temperature are much more important, especially in the two extremes of life. Streptococcus septicemias occur in all regions of the world without special reference to climate, altitude, or season, with the possible exception of the arctic region where all bacterial diseases are rare. In the temperate zones there seems to be a slightly higher incidence during the winter and some indication that it is still more prevalent during the unsettled weather of spring and fall, coexistent with the increase in nasopharyngeal and pulmonary infections.

Streptococcus septicemia is found in all races and both sexes, while no age is immune. However, the infection occurs more commonly in infants, young children and to a certain extent in those past middle age. In the latter, it is very frequent as a terminal infection. Due to the large number of cases of criminal abortion, the incidence of septicemia in young women is much higher than in men of the same age.

Individual susceptibility or resistance has never been proven. Overcrowding as in the cities, particularly in tenement districts, is of some significance not only because of the poor physical conditions which filth, bad ventilation and general unsanitary surroundings engender, but also because of the more frequent opportunities for direct contact transmissions of virulent streptococci and of other bacterial diseases which may open the pathway for a subsequent septicemia. It can in no way be considered an occupational disease, nor one to be especially associated with institutions such as schools, orphanages or prisons. However, due to the epidemics of streptococcus tonsilitis and pharyngitis which frequently infect such a large percentage of the personnel in such institutions, streptococcal septicemias, having the tonsil or pharyngeal lymphatics as the portal of entry, are at times more frequent there and occasionally take on an almost epidemic character.

Toxic agents as drugs, gases, dust, etc., have no special bearing on the disease under consideration. The same may be said of disorders of metabolism and of those factors on which the laity, particularly the patient. always places special stress—worry, mental shock, overwork. or excessive mental or physical exertion.

Trauma is an important etiological agent. The streptococcus finds ready entrance into the body through wounds and abrasions of all kinds. Even the most insignificant injury, as a needle prick, has led to a fatal septicemia. In fact, small penetrating wounds seem to have a greater morbidity from streptococcus septicemia than large, open wounds. In the latter, however, if a considerable amount of lacerated or devitalized tissue is present, the streptococcus has a better opportunity to multiply and increase in virulence than in a cleanly incised wound and the incidence is correspondingly high. The opportunity for extensive thrombosis is also greater and the possibilities for liberation of infected emboli increased.

Epidemics of septic sore throat with a few cases of streptococcus septicemia following have been reported in which the source of contagion was found to be a contaminated milk-supply. It is barely possible that the disease may be transmitted by a contaminated water supply.

Pregnancy plays an important part in the etiology of septicemia, since one of the most fruitful sources of this infection is the uterus after miscarriage, especially so after criminal abortion. There are two important factors leading to this high morbidity,—the anatomical conditions present and the usual lack of any serious attempt at sterility of the external genitals or of the instruments used. From the anatomical standpoint, we have the most favorable condition possible for the multiplication and passage into the blood stream of any pyogenic organisms which may be introduced. The engorged blood-vessels in the uterus are practically large thin-walled sinuses in which infected thrombi readily form and from which emboli easily escape into the uterus and the retained blood-clots and portions of the placenta offer excellent media for the development of highly virulent strains as well as for the rapid multiplication of the organisms. Here, too, the usual protective agents, leukocytes and serum borne antibodies, have little opportunity to attack the clot-protected bacteria.

Chronic alcoholism has been frequently noted in the case histories and undoubtedly plays an important part in the general lowering of the resistance to infection. This appears especially significant in those patients in whom the septicemia is a terminal invasion of the blood stream.

This disease is so frequently associated with some other disease or lesion that purely primary infection is considered the exception, although abrasions and lacerations, often trivial in extent, are common avenues through which the organism reaches the circulation. Second or third degree burns may furnish the portal of entry.

The streptococcus may also enter through various lesions of the skin and subcutaneous tissues such as pustules, carbuncles, erysipelas or a cellulitis. A marked lowering of the general resistance from chronic nephritis, diabetes, or other causes is an important contributing factor with these lesions. The disease also appears not infrequently in cases of chronic osteomyelitis, especially those of very long standing, with amyloid changes in the liver, spleen, and kidneys, and may be caused by the dissemination of organisms during an operation upon the diseased bone.

Numerous acute infections are direct precursors of the septicemia. Notable among these are otitis media with mastoiditis and involvement of the lateral sinus—sinus thrombosis—; acute tonsillitis, acute appendicitis,—especially those cases with thrombosis of the vessels of the meso-appendix—; acute cholecystitis; abscesses of the liver; subdiaphragmatic abscess; peritonitis; purulent inflammation of the joint cavities; streptococcus empyema or a lung abscess; puerperal sepsis; scarlet fever, and influenza. Acute endocarditis is often considered as a primary focus, but is probably the result instead of the cause of a septicemia.

It may appear as a terminal infection with practically all diseases and numerous cases are reported in which the streptococcus is found associated with other organisms in the blood culture. Occasionally several bacteria will be found so associated, but usually only two, although many may be in the primary lesion. The colon bacillus has been most frequently reported, with the staphylococcus a close second. Other organisms discovered with the streptococcus are the bacillus pyocyaneus, the streptococcus mucosus (or bacillus mucosus capsulatus), the diplococcus intracellularis of Weichselbaum, the gonococcus, the micrococcus tetragenous, the bacillus ærogenes capsulatus, the influenza bacillus, and the pneumococcus. The larger number of such mixed infections are terminal but a few have been reported in patients who recovered.

THE ORGANISM.—The streptococcus pyogenes is small, spherical in form, and is usally found in chains of three to twenty or more. It varies in size from 0.5 to 1 *m*. In pus and on some media it freqeuntly appears in pairs as a diplococcus. It stains readily with all the ordinary dyes and is Gram positive. Numerous types have been described, the most important of which are the streptococcus hemolyticus, the streptococcus viridans, and the streptococcus epidemicus. The so-called streptococcus erysipelas cannot be differentiated from the ordinary streptococcus pyogenes and probably is identical with that organism. Numerous other types have been described, based on various cultural characteristics or upon their chemical activity, but the differences are so slight that no one has yet established a satisfactory classification. Certainly for clinical application, the four types mentioned are the only ones of definite importance.

The streptococcus is a strict parasite, but may be carried in a variety of ways. The organism is commonly found in the mouth and nose, and more or less frequently as a skin contamination. Chronic cutaneous lesions, such as those about the nose, back of the ear, axillæ and groin, are often either due to or harbor the organism. It is especially prevalent in the mouth, tonsils and naso-pharynx during the epidemics of colds which periodically recur every fall and winter. No cases are reported of septicemia due to contaminated water supply but numerous observers have noted the occurrence of the disease from infected milk.

MODES OF CONVEYANCE.—The organism is undoubtedly spread both by direct contact with an infected person and by means of contaminated objects. Streptococcus septicemia is not generally considered as a contagious disease in the ordinary sense of the term and fear of a second case of septicemia by near contact is probably groundless. If, however, an abrasion or other open lesions exist through which the organism may enter, then the possibilities of a severe local or general sepsis are great.

Infection through food other than milk is certainly very rare if it exists at all. The milk borne infections often take on the nature of an epidemic. The coccus is undoubtedly spread by contaminated drinking cups and to a certain extent by the dishes in which food is served. Specific instances have been reported where the infection was due to careless unhygienic conditions in the kitchens and to the unsanitary cleansing of the table service. Carriers of virulent streptococci, especially the hemolyticus type, are found in every series of throat examinations.

Before the days of asepsis great numbers of septicemia cases were directly due to the transmission of highly virulent organisms from one patient to another by the hands or instruments of the physician. Among the obstetrical cases the incidence of generalized infection was extremely high.

The organisms may enter the systemic circulation through a large number of avenues. Some of them have been already mentioned under the discussion of associated diseases. Inoculation through cutaneous abrasions or lacerations, even those so minute as to attract no attention, have frequently been the means by which a generalized infection developed. The two most striking examples are septicemias developing from a needle prick or scratch while operating an infected case or at autopsy. No more virulent infections with a higher percentage of deaths have been noted. Furuncles and carbuncles, especially in debilitated individuals, are fruitful sources of generalized infection.

Especially during the epidemics of rhinitis and pharyngitis can cases be expected in which the tonsil is the portal of entry. Mastoiditis, either acute or chronic, may lead to sinus thrombosis with the escape of infected emboli through the jugular. Erysipelas, especially of the face, cellulitis, Ludwig's angina, and abscesses in the nose and mouth are often followed by blood infection. The disease may follow bronchopneumonia, empyema or lung abscess. It has also followed tenosynovitis, abscesses in the fingers or hand, and puncture wounds of the feet. Uterine sepsis, either at the puerperium or following abortion, and appendicitis, especially with peritonitis or thrombosis of the adjacent venous channels, are important etiological factors. Occasionally a generalized infection apparently arises from the gastro-intestinal canal without a demonstrable lesion being present.

TYPES OF INFECTION.—The majority of the cases of streptococcus septicemia run a typical course. The atypical infections may be due to organism of such low virulence that the resulting disease is either so mild that the characteristic symptoms are wholly or partially absent, or the usual course of the malady may be greatly lengthened and a chronic septicemia develop. Minor variations are noted, some strains of streptococcus showing a very rapidly fatal outcome, others show a marked predilection to produce multiple abscess or even a tendency to develop abscess regularly in certain tissues or organs. Other strains will exhibit a striking hemorrhagic picture while some show a tendency to develop endocarditis, meningitis or other rather clear-cut clinical entities. Certain variations in the clinical picture, as a whole rather constant, are associated with certain portals of entry. The most important are those arising from infection in the middle ear and in the puerperal uterus. Mixed infections are occasionally found, the most common being with the colon bacillus and the staphylococcus aureus. It may appear as a terminal infection with practically any disease, but is most commonly associated and with the probable cause of death in scarlet fever, septic tonsilitis and pharyngitis, erysipelas and smallpox. It is also a very serious complication of diphtheria.

Symptomatology.—The incubation period varies from a few hours to two or three days, seldom longer. The only symptoms present are those of the local condition from which the generalized infection spreads.

The onset is usually sudden and characterized by a severe chill promptly followed by a rapid elevation in temperature to 103° F. (39.5° C.) or 104° F. (40° C.) followed by a slight fall. The temperature then rises gradually, sometimes reaching 105° or 106° (40.5° or 41.1° C.). Daily remissions are the rule, but intermissions of 24 to 48 hours or even longer are occasionally noted. Rarely the fever is continuous. The pulse and respirations follow the temperature curve quite closely. The former is usually soft, easily compressible. Hemorrhagic petechiæ, often developing first in the bend of the elbow but showing most abundantly on the chest and abdomen may appear, especially when the septicemia is due to the streptococcus hemolyticus. With the other types of streptococcus infection cutaneous lesions may consists of a simple rash or be wanting throughout the disease. Severe hemorrhage from the intestines may take place and the author saw one death from this cause within ten hours of the onset of the septicemia. Delirium or marked mental apathy may appear early.

Streptococcus septicemia of puerperal or abortion origin is characteribed by frequent chills, usually daily, but which may occur twice or more in twenty-four hours or appear only on alternate days. The chills are followed by a sudden rise in temperature with a correspondingly rapid fall, profuse perspiration and marked prostration. Delirium, especially while the fever is high, followed by extreme mental apathy or a semi-comatose condition usually appears in a few days. Metastatic abscesses frequently develop.

Streptococcus septicemia of otitis origin is characterized by the more or less regular, wide fluctuations in temperature, generally associated with severe chills. Delirium is usually an early sign and symptoms of meningitis are frequently noted. Marked dyspnea and cyanosis are present during the chills. As the disease progresses the patient becomes drowsy, apathetic and finally semi-comatose. Cutaneous lesions are rare.

Physical Findings.—On physical examination an enlarged spleen is frequently felt. The liver is more rarely enlarged, but when it is jaundice is a frequent accompaniment. The primary lesions may show increased signs of inflammation and a serosaguineous pus rather typical of the streptococcus. On the other hand, no evidence of increased local infection may be noted. In cases of septic sore throat a membranous tonsillitis may confuse the observer as the resemblance to a diphtheritic membrane is striking. However, in streptococcal infections there is usually a peculiar, disagreeable odor to the breath, and nasal examination will disclose a thin, bloody, serous discharge. In otitic cases the discharge from the ear may cease, but increased tenderness on palpation over the mastoid and swelling back of the ear indicate an extension of the purulent process. Puerperal cases will show a boggy uterus, delayed involution, and profuse lochia. The lower abdomen is sensitive to pressure and sometimes has a doughy feeling due to pelvic cellulitis. The physical findings of the various complications such as endocarditis or bronchopneumonia do not differ from those found in other diseases.

LABORATORY FINDINGS.—The blood examination usually shows a mild anemia with a moderate leukocytosis. Much depends upon the rapidity with which the case develops. In the fulminating type very little blood change may be noted, the leukocyte count averaging about 11,000 and being below normal at times, particularly in debilitated subjects. Those cases in which severe hemorrhage develops will show a corresponding anemia. If the disease lasts for a week or more the red count may be reduced to 2,000,000 or 3,000,000 with a corresponding low hemoglobin. The leukocyte count may rise to 18,000 to 20,000 with a differential count showing 85 per cent. or more of polymorphonuclear leukocytes. So much depends upon the amount of suppuration in the primary lesion that the records of blood examination are of necessity unsatisfactory and are probably of little diagnostic value from the septicemic standpoint.

Blood culture is of great diagnostic importance. It should be repeated at frequent intervals to determine definitely both the actual presence of a septicemia and the causative organism. At times the streptococcus will be found in the peripheral blood after a chill and this should be borne in mind when repeated negative cultures are reported. Rarely the organisms will be found in a stained slide such as is made for the differential count. The author saw one such case where numerous chains of streptococci were found in the blood obtained from the lobe of the ear. This was a rapidly fatal case, developing from a slight abrasion on the nose.

The urine will show a moderate amount of albumen, a high specific gravity and frequently granular casts. Pus cells are often present. In a limited number of cases the streptococcus can be cultivated from the urine.

No characteristic changes have been reported in the stomach contents nor regularly in the feces. Where severe diarrhea exists, large numbers of streptococci may be found in the stools. This observation is of particular significance in the epidemics of supposedly mild bone infections.

The streptococcus may be found in large numbers and sometimes in practically pure culture in the nasal secretions and pus from the middle ear when those parts are involved in the disease process. The pus is often quite distinctive, being a thin, sero-sanguineous fluid without odor. Pus from abscesses within the body is usually thicker and of a yellowish color. The organisms will be found in large numbers, both on smear examination and by culture in all abscesses and in the serous fluid in peritonitis, pleuritis, pericarditis and synovitis.

Diagnosis.—Streptococcus septicemia should be suspected in all cases in which without evidence of pulmonary complications a sudden chill with a rapid rise in temperature follows a wound or appears during the course of septic sore throat, otitis media, scarlet fever, diphtheria, influenza, appendicitis, or other of the common etiological factors. The recurring chills and high fever with daily remissions or intermissions, early delirium or mental apathy, and the appearance of marked prostration indicate a septicemia, probably of the streptococcus type. The absence of acute gastro-intestinal symptoms and a cutaneous eruption, the presence of which are quite characteristic of pyocyaneous septicemia, and of severe pains in the shoulders, arms, or larger joints, symptoms commonly found with the staphylococcus septicemia, aid in the differential diagnosis. According to Osler, the streptococcus infection is further differentiated from the staphylococcus by the absence in the latter of delirium, by a rather marked mental acuteness and by a greater anemia.

Although the temperature may remain rather high and be without the usual marked daily remissions which, together with the enlarged spleen, might suggest typhoid fever, the severe rigors and leukocytosis of streptococcus septicemia will serve to distinguish the two.

The final diagnosis must rest on the laboratory findings. Blood cultures should be repeated until a positive result is obtained. Even in the absence of a positive blood culture, the presence of streptococci in metastatic abscess is sufficient to establish the diagnosis.

Complications.—The majority of cases of streptococcus septicemia are so fulminating in type that complications are largely absent. The circulating organisms may, however, set up an acute inflammatory process in any tissue with which they come in contact. We may have brain abscess, single or multiple; meningitis; mastoiditis; accessory sinusitis; acute purulent thyroiditis; bronchopneumonia; lung abscess; pleural empyema; pericarditis; endocarditis; peritonitis; abscesses in the liver, spleen or kidneys; purulent synovitis; osteomyelitis, particularly of the long bones; and intramuscular or subcutaneous collections of pus, occasionally thrombosis of important vessels takes place, or emboli plug their lumen leading to gangrene of the extremities. Severe hemorrhages from the intestine are occasionally a serious complication. The site of the portal of entry seems to play an important part in the localization of the various omplications. Thus the tonsil infection shows a marked tendency to produce an endocarditis; cutaneous lesions have a predilection to localization in the long bones; uterine infection more often produce multiple abscess, especially in the liver, spleen and kidneys.

The number of cases which survive is not great, but of those which do, the greater number recover completely. Chronic osteomyelitis is probbly the most common sequela. Chronic valvular disease following the acute endocarditis is next in frequency. A small percentage continue to suffer from chronic empyema, chronic cholecystitis and from middle ear disease. Chronic nephritis occurs especially after scarlet fever which was associated with a streptococcus septicemia.

Association with Other Diseases.—A streptococcus septicemia is commonly associated with septic sore throat and scarlet fever. During certain epidemics of influenza it was found in a high percentage of the fatal cases. Rather rarely a mixed septicemia—streptococci associated with staphylococci, bacillus coli, pneumococci, or bacillus pyocyaneus—is found by blood culture.

Treatment.—General prophylaxis consists largely in the avoidance of contact infection, especially during the epidemics of septic sore throat, scarlet fever and influenza. The same measures used to control the common contagious diseases are applicable here. For the individual much can be done to prevent the initial local infection or to limit its extension by strict asepsis in all surgical procedures, adequate debridement in all contaminated wounds, and early diagnosis and operation in such conditions as acute appendicitis, peritonsilar abscess and mastoiditis. Since the organism in practically every uterine infection is introduced from without, the most careful aseptic technic must be used when dealing with the pregnant uterus. The employment of trained physicians in place of midwives in all obstetrical cases would do much to reduce the annual mortality from septicemia. Vaginal examination might better be replaced by rectal, both before and during labor. Criminal abortions, one of the most fruitful sources of streptococcus septicemia, cannot be prevented, but the number can undoubtedly be reduced by vigorous prosecution of the offenders and by educating the public to the grave dangers to which they are subjected.

The early recognition of lateral sinus involvement during a middle ear or mastoid infection, followed by the proper surgical procedures will not only prevent a large number of septicemias but will cure many already developed.

The active treatment of streptococcus septicemia embraces both general and local measures. The general condition must be bolstered up by a **simple, nourishing diet, absolute rest** and **fresh air.** It has been shown that cheerful nursing, pleasant, well-lighted, well-ventilated rooms and the **avoidance of all unnecessary examination** does much to improve the patient's mental attitude and reflexly the nutrition. **Liquids** should be forced and if the patient refuses to take fluids in adequate quantity by mouth, they should be given **by rectum** or if necessary **subcutaneously.**

Vaccines, both autogenous and polyvalent stock preparations have been extensively used with widely varying results. Without doubt the **autogenous vaccine** should be used, whenever time for its preparation permits, in preference to a vaccine which may not contain the particular strain of streptococcus needed. The vaccine is given at intervals of two to five days, usually starting with an initial dose of **one hundred million** and rapidly increasing to **one thousand million.** Brilliant results are reported by some authors, but equally brilliant results are seen without vaccine treatment. No adequate comparative statistics are available to prove or disprove the value of vaccines in this disease and until more complete, comprehensive studies are made, it will remain for the judgment of the individual physician, whether or not he shall make use of this therapeutic agent.

Antistreptococcus serum stands today in much the same position as the vaccine. Some authors report very favorable results following its use. Others fail to get any benefit and some, in fact, are inclined to think that the serum actually does harm through the severe reactions which sometimes follow its use, and the added burden the foreign protein throws on an already overburdened economy. A number of favorable reports have been published regarding the **combined use** of an **antistreptococcus serum** and a **streptococcus vaccine.**

It is pretty well accepted by all that if an antistreptococcus serum is to be of much value it must be given early in the disease and in large quantities. A **polyvalent serum** is a necessity since the organism varies so greatly in its immunity reactions. The serum should be fresh, as deterioration in its protective properties has been shown to progress rapidly. Stengel has had the most satisfactory results when using a serum within twenty-four hours after its withdrawal from the horse. Some unfavorable reports may be the results of using old serum. However, the age of the serum has not been mentioned by the majority of those who recommend it highly and even when old if used in sufficient doses may at times be of benefit. Until a large number of parallel cases treated with and without antistreptococcus serum are published the opinion as to its therapeutic value will remain in the balance. On the whole, judging from the recent literature, the tendency is in its favor. The dosage varies with the age of the patient and the severity of the case,—**20** to **200 c.c.** of the **antistreptococcus serum** given **subcutaneously** or **intravenously** each day or more often if the symptoms so warrant. It has no prophylactic value.

Serum from convalescent patients have been given and excellent results reported. The larger number were cases of scarlet fever with the streptococcus as the complicating agent. Bryan reported an interesting case in which a child of two years had a streptococcus infection following an operation. A vaccine was used without benefit. However, the surgeon contracted the infection from the patient and was treated with the same vaccine with prompt recovery. The convalescent serum from the surgeon was then administered to the child resulting in rapid improvement and eventual recovery.

Blood transfusion is a very valuable therapeutic agent in chronic or semi-chronic cases of septicemia. Here its value lies not in any specific effect, as the antibodies normally present are of little value against the streptococcus, but in its general stimulating effect and especially on the improvement of the anemia. Small quantities, **two** to **three hundred cubic centimeters**, repeated **once** or **twice a week** is of as much if not more value than a larger amount at longer intervals.

In the acute cases, the value of blood transfusion is still debated, some authors considering it the most important therapeutic agent at their command. Others claim it is not only useless but may, through the increase in the volume of circulating blood and of the blood pressure, spread the infection even more widely. This may be due to the breaking off of infected thrombi and the transportation of the emboli to tissue previously uninvolved. Certainly in some cases the disease process seems to flare up after a transfusion. Possibly the type of infection may be a clue to the disparity in the published results since the majority of favorable cases have been those associated with either scarlet fever or sinus thrombosis. In the septicemias of the puerperium and after criminal abortion the results on the whole have been very disappointing.

Colloidal silver, administered either subcutaneously, intramuscularly or intravenously, has been highly recommended, but the results have been far from uniform and in the majority of clinics its use has been largely abandoned. Numerous other clinical compounds, including mercuric chlorid, formaline and eusol have been tried and thrown into the discard.

[Arsenical preparations, as sodium cacodylate, salvarsan, neo-salvarsan, and others of the same group, are advocated by some who report favorable results. *Ed.*]

The surgical indications arise largely from the complications and sequelæ. It is important, whenever possible, to **eradicate** the **primary focus** or, at least to institute adequate drainage. The most favorable portal of entry from the surgical standpoint is the thrombosis of the lateral sinus of otitic origin. The early exposure and drainage of the sinus give very gratifying results. In the infections of puerperal origin numerous operations including ligation of the uterine veins and hysterectomy have been advocated in times past. At present, however, the tendency is toward very conservative measures—**hot vaginal** or **uterine douches** and at most the removal of retained secundines.

The various complications call for a diversity of operative procedures which cannot properly be described here. In general it may be stated that all abscesses should be drained and that special lesions, such as an acute appendicitis, demand operation in spite of the presence of a general infection. Collections of serous fluid in the various joint cavities should not be opened unless the distension and pain demand some relief. In such an eventuality the fluid should be removed by aspiration under the strictest aseptic precautions. The collection of fluid in the thoracic cavity may cause embarrassment of the heart and lungs in which case aspiration should be done, but under no circumstances should the chest cavity be opened by incision until actual pus is demonstrated. The mortality following early operation for streptococcus empyema while the fluid is still of serosagineous nature was appallingly high during the last influenza epidemic.

The convalescence may be rapid or long drawn out. Much may be gained by an abundance of nourishing food prepared and served in an appetizing manner. Fresh air and sunlight are valuable therapeutic aids.

Prognosis.—The prognosis in streptococcus septicemia is always grave. Few diseases have such a high mortality rate, which in many series run 75 per cent. The death rate may be even higher, and again in a few cases, a mortality of only 25 per cent. will be recorded. The prognosis is most favorable in cases of otitic origin where proper surgical procedures have been carried out. It is probably most hopeless where the septicemia is associated with diphtheria, scarlet fever or smallpox. Patients who survive the infection usually make a complete recovery. A few cases may be left with a chronic nephritis, chronic valvular trouble, or a chronic osteomyelitis.

Pathology.—At autopsy, practically every lesion which may be produced by any pyogenic organism has been found. The more common are: purulent meningitis; cerebral and cerebellar abscesses; pharyngeal and peritonsillar abscess; frontal sinusitis; otitis media; mastoiditis; labyrinthitis; lateral, straight, cavernous and superior longitudinal sinus thrombosis; acute thyroiditis with abscess formation; purulent bronchitis; bronchopneumonia; multiple lung abcesses; thoracic empyema; pericarditis; ulcerative endocarditis; myocarditis with multiple abscesses; acute hepatitis; multiple abscesses in liver; acute hemorrhagic gastritis and enteritis; acute pancreatitis; perinephritic abscess; acute hemorrhagic nephritis; pyonephritis; pyelitis; cystitis; ovarian abscess; purulent salpingitis; abscesses in uterus; purulent peritonitis; appendicitis; abscesses in testicle, prostate and seminal vesicles; osteomyelitis of nearly all bones, but esecially of the femur, tibia and humerus; purulent synovitis; myositis with abscess formation; subcutaneous abscesses; cutaneous and subcutaneous hemorrhages. Certain pathological findings are indicative of the different strains of streptococci. An excellent example is the rapidly spreading, ulcerative vegetations on the heart valves in hemolyticus septicemia in contrast with the small, flat, grayish-green masses on the mitral valve in the viridans infection.

Microscopically the lesions found are both suppurative and toxic in origin. In the brain, petechial hemorrhages, edema and granular degeneration of the nerve cells may be found as well as areas of softening, sometimes the result of infarcts, and multiple abscess, usually caused by infected emboli. The lungs show edema in the alveolar walls and the spaces are more or less filled with leukocytes, epithelial cells and red corpuscles. There is considerable round cell infiltration and the dilated vessels contain a large number of leukocytes. Certain areas show complete collapse of the alveolar spaces. Abscesses varying from microscopic size to two or three inches in diameter are noted rather frequently. The streptococcus hemolyticus produces a bronchopneumonia characterized by its extreme hemorrhagic tendency and the usual limitation of the lesion about the bronchi. Large emboli causing abscess or gangrene of the lung and occurring most frequently in septicemias of puerperal origin produce at first a hemorrhagic infiltration followed by necrosis and liquefaction.

The heart shows cloudy swelling and fatty degeneration, infiltration with round cells and leukocytes, and in cases of some duration marked proliferation of the connective tissue. Microscopical and larger collections of pus are seen in the heart muscle. The valves may show edema, leuocytic and round cell infiltration, fibrinous deposits, necrosis and ulceration. Masses of streptococci may be seen in the superficial layers of the endocardium.

The liver shows cloudy swelling, fatty degeneration, areas of necrosis leading to multiple suppurative foci, round cell and leukocytic infiltration and increase of the connective tissue. Thrombosis is seen in the capillaries and smaller arterioles which may be filled with pus. Large numbers of streptococci are found in the blood-vessels and interstitial tissue.

The kidney shows parenchymatous degeneration, cloudy swelling, particularly in the convoluted tubules, marked fatty transformation. Multiple areas of necrosis of varying sizes and containing enormous numbers of streptococci may be found throughout the kidney but more abundantly in the cortex.

The microscopical picture in the other tissues of the body is not characteristic, but is simply that of an acute suppurative lesion.

The pathological findings in streptococcus lesions differ from those of the staphylococcus chiefly in the widespread character of the former, both vascular and lymphatic systems being involved and serving as carriers of the infection, and in the greater severity of the toxic reactions.

STAPHYLOCOCCUS SEPTICEMIA

Definition.—This condition is a generalized blood-borne infection due to the staphylococcus.

Etiology.—PREDISPOSING CAUSES.—The incidence of staphylococcus septicemia does not seem to be related to changes in temperature, climate or season. It is found in all races, at every age, and in both sexes without any noticeable predilection for any group. A general lowering of the resisting powers through undernourishment, excessive physical strain as in soldiers during active warfare, or preexisting disease is an important contributing factor. Occasionally the staphylococcus is found associated with some other organism in the production of a septicemia. The most common mixed infections are with the colon bacillus and the streptococcus. Much more rarely it has appeared with the bacillus pyocyaneus, the pneumococcus and the gonococcus.

Staphylococcus septicemia is commonly associated with boils and carbuncles since these are frequently the original focus from which the infection spreads. In a secondary way it may be associated with debilitating diseases as chronic nephritis, diabetes and chronic alcoholism. Chronic focal infections such as pyorrhea, root abscesses, tonsilitis and accessory sinus infections seem to play a small part, if any, in the incidence of the disease and their association would probably be largely incidental.

EXCITING CAUSES.—Three noteworthy forms of the staphylococcus have been recognized; the staphylococcus pyogenes aureus, albus, and citreus. The first type is by far the most important and is the one usually found as the causative agent in pyogenic processes. The albus type is as a rule of low pathogenicity. Staphylococcus citreus is the least common and has the lowest virulence of the three forms. They are distinguished by the color of their colonies on solid media. aureus producing a golden yellow, albus a white, and citreus as brilliant lemon color. The organisms are spherical, 0.5 to 1 micron in diameter, without spore formation and without motility. They stain readily and are Gram positive. Although usually found in clumps they may occur in pairs and on superficial examination be confused with diplococci. The organism grows readily on all ordinary media, best at a temperature of 25° to 35° C. (102.6° to 120.6° F.).

The staphylococcus albus is found on the skin of all individuals and frequently in the various body orifices. The distribution of staphylococcus aureus is similar but it not so universally encountered. The latter is the most common etiological agent of acne, furunculosis and of carbuncles and is the usual type found in staphylococcus septicemia. The organism is found only on the bodies of man or the lower animals, their secretions or exceretions, or on material recently contaminated by them.

Several severe epidemics of acute gastro-intestinal disorders with undoubted systemic infection have been traced to a contaminated milk supply. No report of an epidemic due to other foods or to the water supply has been noted by the author and if such dissemination does take place it must be of rare occurrence.

Contact infection is certainly the rule, although contaminated instruments, dressings or the hands of attendants may transmit the infection. The organism may enter the blood stream through cutaneous or subcutaneous infections as boils and carbuncles,—through abrasions, lacerations, burns or infections in the ear, the nose, accessory sinuses, the tonsils, the gastro-intestinal tract, the uterus, the urethra, and possibly the lungs. Since the organism is nearly always present on the skin of the healthy individual, local and systemic infections do not of necessity depend upon the transmission of staphylococci from another individual. However, the virulence of various strains differs considerably and the most severe and rapidly fatal septicemias are often acquired by direct contact or inocculation from an individual already seriously ill with a local or generalized infection due to the same organism.

No special types of infection are noticeable as gradients may be readily found between the mildest and the most severe. Mixed infections are occasionally noted, particularly with the streptococcus and the colon bacillus. As a terminal infection, staphylococcus septicemia is not of as great importance as that due to the streptococcus. Routine bacteriological examinations at autopsy would in all probability show a higher percentage of terminal staphylococcus infections than is generally realized.

Symptomatology.—The period of incubation is not known but is undoubtedly very short, perhaps only a few hours in the fulminating cases. The onset is usually characterized by a chill followed by fever and profuse sweating with lancinating pains in the muscles of the arms and legs or larger joints, as the shoulder. There may be slight swelling about the joint and the arm or leg may be very painful to pressure. Headache, nausea, and vomiting are absent or of little severity in the majority of cases. The onset may be gradual without chill, the patient complaining only of a moderate headache and pain in the shoulder, arms, wrists and hands. Even the latter symptoms may be wanting, the disease making itself manifest only by the high, continuous or remittent fever.

The septicemias of gastro-intestinal origin differ considerably in their initial symptoms. Here the disease is ushered in by an acute gastro-intestinal syndrome consisting of nausea, vomiting and frequent mucous stools. Often blood is noted mixed with the mucus. Headache and backache may be severe and prostration was an early sign in the majority of cases. The temperature varies, usually rising rather rapidly to 103° or 104° F. (39.6° to 40° C.). In the series reported by Farnell and Harrington marked neurolitic symptoms developed some times very early in the disease. These consisted of severe pains in either or both the upper and lower extremities apparently due to a peripheral neuritis. Some patients had excessive pain on slight pressure, others only on deep pressure over the muscles or nerve trunks. Marked weakness to complete paralysis was noted in a large number. The reflexes were frequently absent on one or both sides, especially the patellar and the Achilles reactions.

Early in the disease the mentality is unusually unimpaired and may appear hyperacute. Later in the severe cases the patient usually becomes irrational, delirious and finally passes into coma. The mental clearness may, however, persist to the end whether it be death or recovery. As the disease progresses the presence of a profound sepsis is shown by the severe chills, wide variations in temperature, anemia, thready pulse, and apathetic facies. Severe chills occur once or twice a day followed by a sudden rise in temperature to 104° to 106° F. (40° to 41.1° C.) succeeded by a sudden drop to subnormal levels with profuse perspiration. In the cases of gastro-intestinal origin the chills were not such a conspicuous feature and in some individuals were entirely absent.

Metastatic abscesses occur in a large per cent. of the cases and may change the clinical picture remarkably. Thus, a metastatic pneumonia may obscure the other symptoms of a septicemia or a brain abscess or meningitis may focus the clinician's attention upon the central nervous system. In the more chronic cases abscesses commonly develop in the muscles, joints and subcutaneous tissues.

A cutaneous rash characterized by petechial or fine vesicular eruptions especially over the thorax and abdomen is noted rather frequently. The vesicles which vary from pinhead to three or four millimeters in diameter are filled with a clear serum and surrounded by a red areola. In a short time the clear serous fluid changes to a thick yellowish pus. Petechial hemorrhages may be very numerous over the body and to a somewhat less extent over the face and extremities. Pinpoint hemorrhages have been noted in the conjunctiva. More rarely subcutaneous hemorrhages and a bronzing of the skin, particularly of the face, are seen.

The blood-picture is that of a rather severe secondary anemia with a moderate leukocytosis. The average red cell count is about 3.000.000 and the hemoglobin 35 to 48 per cent. The leukocytes vary from 10,000 to 14,000 per cu. mm. Without metastatic abscesses, the course varies little although in one fatal case it dropped to 3,800. The differential count shows from 70 to 92 per cent. polymorphnuclears with about 4 to 6 per cent. small and 4 to 6 per cent. large lymphocytes in the average case. There is no increase in the eosinophils.

A blood culture should be taken in every case as a definite diagnosis can be obtained by this method in the majority of cases before metastatic abscesses develop. The number of colonies, which have been noted as high as 100 per cubic centimeter of blood, may have some prognostic value although sufficient data has not yet accumulated on which to base any definite conclusions.

The urine is not characteristic and will be found to vary in accordance with the severity of the symptoms as in most febrile conditions. The specific gravity ranges from 1020 to 1200, depending largely upon the fluid intake as does the color which varies from straw to dark amber. No sugar will be found, but a few fine granular and hyalin casts may be present. In the severe infections the granular casts may be numerous and considerable albumin found. The presence of pus in the urine suggests a pyelitis or pyelonephritis. In such conditions the white cells may be in such quantity as to give a distinct cloudy appearance. Frequently, even in the absence of demonstrable kidney involvement the staphylococcus may be cultured from the urine and may be of considerable diagnostic importance.

The feces, except in the cases of gastro-intestinal origin, show nothing of interest. In the milk-borne infections, however, the organism may be found in the stools in enormous numbers. Under such circumstances a clinical diagnosis may be made before the blood culture proves positive.

Diagnosis.—The presence of a staphylococcus septicemia should be seriously considered in all cases of high, continuous or remittent fever, clear mentality, rapidly developing anemia and pains in the muscles of the arms or legs, or the larger joints. The condition has been confused with acute articular rheumatism but the general toxic manifestations are much greater in septicemia, while the characteristic rheumatic swellings are largely absent. The presence of petechial or vesicular eruptions is of great diagnostic value. Perhaps the most suggestive of all physical findings is the development of subcutaneous and intramuscular abscesses, in fact staphylococcus septicemia is characterized by the extreme frequency of secondary foci. Chills followed by a profuse sweating are rarely absent and of much significance.

Gastro-intestinal symptoms are largely wanting except in those cases due to food—particularly milk—contamination. Here the extreme diarrhea is associated with nausea, vomiting, pain in the head and back, profound prostration and frequently with neuralgic pain in the extremities and paralysis.

The final diagnosis is made in the laboratory. Cultures should be taken of the pus from metastatic abscesses, of the urine, diarrhea stools, and the blood. The presence of the organism in the urine is suggestive but not of definite diagnostic value. The significance of staphylococci in the feces depends upon their number and the presence of gastro-intestinal symptoms. The two most important findings are the cultures from the metastatic abscesses and the blood. Either is sufficient to make a positive diagnosis of staphylococcus septicemia.

Complications are numerous, the most important of which are: abscesses in the cutaneous or subcutaneous tissues, skeletal muscles, heart, lungs, liver, spleen, kidneys, and brain; acute endocarditis; and acute osteomyelitis. Less commonly a staphylococcus pneumonia, empyema, pericarditis, peritonitis, perinephritic abscess or meningitis is seen.

Practically all cases of acute osteomyelitis are due to the staphylococcus entering the bone marrow by way of the blood stream. This may occur during the septicemia or without a septicemia actually being present. In the later case it may result secondarily in a septicemia.

Acute endocarditis with the production of ulcerations and vegetations on the pulmonary and mitral valves occur more frequently than in streptococcus septicemia. Miliary abscesses in the kidney are of common occurrence but may remain undiagnosed except at autopsy.

The most serious and most common sequela is chronic osteomyelitis. This is found in the majority of patients who had any acute bone involvement during the course of the septicemia. Much can be done to prevent chronic osteomyelitis by the early diagnosis and early, adequate, operative treatment of the acute bone infection. The long bones are usually involved, particularly the femur and tibia. Metastasis to the bone with the development of acute osteomyelitis is characterized by acute localized pain, increased by pressure over the bone involved. The leukocytes may rise rapidly to 30,000 or even higher.

Staphylococcus septicemia may be associated with diabetes, chronic nephritis, chronic alcoholism and chronic osteomyelitis. The organism may be associated with streptococci, pneumococci, the bacillus pyocyaneus or the colon bacillus in the production of a mixed septicemia.

There are only two clinical varieties of note. The first has the portal of entry usually in the skin and is chracterized by high fever, chills, lacinating pains, in the muscles and joints, but without much headache and with a comparative absence of nausea, vomiting or diarrhea. In this group, metastatic abscesses are very common. This type may be further divided into two subvarieties: an acute fulminating disease and a chronic or more or less subacute form.

The second variety is of gastro-intestinal origin and is characterized by severe nausea, vomiting and diarrhea, associated with headache, backache and at least in some epidemics with neuralgia pain and paralysis. The prostration is of even greater severity than in the former type.

Treatment.—PROPHYLAXIS.—The epidemics as well as the sporadic cases of milk-borne infection can be entirely prevented by routine pasteurization or sterilization of the milk supply. Since the value of this procedure is becoming well recognized by the public and is insisted upon in the majority of institutions, the incidence of the gastro-intestinal form of staphylococcus septicemia will rapidly decline and cases in the future should be of extreme rarity.

The prevention of boils, carbuncles and other staphylococcic infections is much more difficult. However, much has been done in the larger factories to prevent the spread of cutaneous infections by the instillation of modern lavatories and paper towels, and particularly among machinists by the heat treatment of the oil which flows from one machine to the next. Here the use of steam or other forms of heat to sterilize the oil in the receiving tanks before it is again pumped back to the machines has reduced the number of cutaneous infections among the workingmen to a minimum. Adequate incisions for drainage of boils and the complete excision of carbuncles undoubtedly reduces the incidence of septicemia.

If every case of acute osteomyelitis was recognized early and modern surgical treatment promptly instituted, one of the most fruitful sources of staphylococcus septicemia would be obliterated. This can only be accomplished by further enlightenment of both the general physician and the public, the former that he may more frequently make a correct, early diagnosis, and the latter that all pains of children are not necessarily "growing pains" or rheumatism and that a competent physician or surgeon should be consulted at once. When the gravity of the disease is recognized and the pitiful condition of the neglected case understood, much of the family objection to operation and the hospital care of children will disappear.

SPECIFIC MEASURES.—It is essential that the **primary focus be removed** or **adequately drained** whether it be a boil, carbuncle or an osteomyelitis. The **secondary abscesses** should likewise be **treated surgically**, the appropriate technic depending upon the location of the pyogenic process but differing in no way from the usual, accepted procedures for the drainage of pus in the respective regions.

General supportive measures such as **absolute rest, adequate nutri-**

tion, forced fluids, fresh air and **careful nursing** should be insisted upon. Several authors have reported excellent results following **blood transfusion.** However, there are equally discouraging results reported by others and for the time at least we must consider the question undecided as to the value of blood transfusion.

VACCINES.—Brilliant results are some times obtained, apparently due to the use of **vaccines. Autogenous cultures** are, of course, preferable, but not as essential as in the streptococcus infections, since the staphylococcus does not vary so remarkbly in the immunity reactions. The initial dose is usually one hundred million killed organisms, rapidly increasing the number until one thousand million are given at each injection. An interval of three to five days is considered best. The vaccine treatment should be continued until all evidence of the continued activity of the disease disappears. This will be evidenced by the cessation of fever, the absence of new metastatic foci and the return to normal leukocytosis.

Prognosis.—The prognosis is always grave. In large series of cases the mortality runs from 68 to 75 per cent. At the two extremes of life the death rate is even higher. Much depends upon the general condition of the patient and the source of the infection, those of osteomyelitic origin being the most favorable, the mortality being as low as 40 per cent. On the other hand, a generalized infection developing from a boil or carbuncle is extremely grave and the average mortality is well over 90 per cent. In the author's experience the presence of diabetes, chronic nephritis or chronic alcoholism has given a particularly unfavorable prognosis.

The future of those cases which recover but have a persistent osteomyelitis is anything but rosy. Modern surgical practice, especially the saucerization of the infected medullary cavity, the removal of all sequestra and diseased bone, no matter how extensive the process, and the use of Dakin's solution, gives a much higher percentage of cures in osteomyelitic cases than formerly. But the marked tendency for the condition to recur or to develop later in another bone makes the outlook doubtful. The extensive deformity which may be left as well as the possible development of amyloid changes in the liver, spleen and kidneys should not be forgotten when the ultimate prognosis is given.

Pathology.—The gross changes found at autopsy are: multiple cutaneous and subcutaneous abscesses; single and multiple abscesses in the brain; purulent meningitis; ulceration of septum and turbinates; abscess of epiglottis; purulent pneumonia; pulmonary edema; large abscesses and military abscesses in lung; empyema, purulent pericarditis; military abscesses in heart muscle; ulcerative endocarditis; ulceration and vegetations on mitral and pulmonary valves; purulent peritontitis; fatty liver; large and small abscess of liver; infarcts of spleen; miliary abscesses in spleen; miliary abscesses in ileum; acute hemorrhagic gastritis and enteritis; perinephritic abscesses throughout kidney substance; pyelonephritis; cystitis; prostatic abscess; osteomyelitis of all bones but particularly of the femur, tibia and humerus; purulent synovitis; purulent bursitis; and abscess in skeletal muscles.

The microscopical findings in addition to those noted in the gross examination are: petechial hemorrhages between nerve bundles in the spinal nerves; local areas of necrosis in brain; thyroiditis; purulent bronchitis; hemorrhagic infiltration, edema, necrosis and infarcts in lungs; areas of necrosis in heart muscle; subepicardial hemorrhages; passive congestion; cloudy swelling, local necrosis, hemosiderin pigmentation and fatty degeneration in liver; fibrosis, infarction, necrosis and polymorphonuclear cell collections in spleen; marked cloudy swelling, necrosis and infiltration with polymorphonuclear cells, collection of staphylococci and hemorrhages in the tubules of the kidney; congestion, necrosis and hemorrhages in the adrenals; necrosis, infiltration of leukocytes, and bacterial collections in prostate; hemorrhagic ulcerative cystitis; hemorrhages in mucosa and submucosa of intestines; necrosis, leukocytic infiltration and hemorrhages into skeletal muscles.

COLON BACILLUS SEPTICEMIA

Definition.—Colon bacillus septicemia is a febrile disease, some times closely resembling paratyphoid fever, due to a generalized infection with the bacillus coli communis.

Etiology.—Predisposing Causes.—The disease occurs at all ages and in either sex and its incidence is apparently not influenced by ordinary external conditions such as extremes of temperature, climate, or social conditions. A more or less general lowering of the resistance to all infections as is found in chronic alcoholism, chronic nephritis, diabetes, malignancy and other wasting diseases is noted in many of the cases, but certainly is a contributory factor of no great importance.

Bacteriology.—The bacillus coli communis is a rod-shaped motile organism, staining readily with ordinary anilin dyes. It is Gram negative, grows rapidly on ordinary culture media and in the presence of glucose produces gas. It is a normal inhabitant of the intestinal canal where it is purely a saprophyte and ordinarily has a very low virulence. The organism occurs on the skin purely as a contamination. Outside of the body it is commonly found in contaminated water and milk supplies. Since the organism is universally present, the possibility of transmission of a virulent strain from one person to another, either through direct contact or through intermediary agencies, is difficult of proof and the usual supposition is that a colon bacillus septicemia is due to the increase in virulence of organisms normally present in the individual.

The bacilli may gain entrance to the general circulation through defects in the intestinal mucosa, as in ulceration, perforation, appendicitis, strangulation in a hernial sac, volvulus or mesenteric thrombosis. It may also enter through wounds, especially operative wounds about the perineum, through infected thrombosed hemorrhoids, through a traumatised urethra and through the biliary tract. In the latter, the primary disease is more often a chronic than an acute cholecystitis. Before the present two-stage prostatectomy operation the author saw a number of colon bacillus septicemias follow enucleation of the prostate. Rarely the organism enters through the vagina or infected uterus.

The disease varies greatly in its severity, depending largely, no doubt, upon the virulence of the particular strain causing the infection. Many cases of temporary or intermittent colon bacillus bacteræmia exist without signs of a systemic infection. From this comparatively symptomless group, a series of cases may be found which show a gradual increase in the gravity of the disease until the severely toxic, rapidly fatal cases are reacted. The colon bacillus produces a certain number of terminal septicemias, probably a much larger number than is generally realized. Some authors consider three types of colon bacillus septicemia; First, resembling typhoid; second, with secondary abscesses; third, a terminal infection. Winckel's disease is a rapidly fatal septicemia of the new-born due to the bacillus coli.

Symptomatology.—The period of incubation is not definitely known, but apparently may be only a few hours in some cases. In others, with a more protracted period, the symptoms may consist of malaise, anorexia and a slight headache. Other patients may complain of severe pain in the head, back or extremities, or of chills, night sweats and general weakness.

The onset is usually sudden and characterized by severe frontal headache, anorexia, vomiting and sometimes acute pain in the back or abdomen. The temperature rises rapidly, reaching 103° to 104° F. (39.6° to 40° C.). A severe chill may precede the fever. Profuse perspiration and marked prostration usually accompany the fever. Death may occur in forty-eight hours or the pyrexia continue for five to seven days when it gradually falls to normal and the systemic symptoms disappear. After an interval of seven to fourteen days, a sudden chill, high temperature, profuse sweating, nausea and vomiting usher in a second period of five or six days the symptoms of which are like the first. These relapses occur with much regularity and may persist for eight to ten or more weeks. During this period there is usually a steady downward trend of the patient's general condition. Emaciation becomes more marked, a severe anemia is practically always found, and eventually death from toxemia takes place. From the first the mentality is usually dulled and during the relapses the patient may lie in a semicomatose state. Headache may be severe and constitute the chief complaint.

In contrast to the above clinical course, many patients from the beginning have a daily chill followed by a high fever which may last only one to two hours, succeeded by profuse perspiration and a normal or subnormal temperature. The chills may be even more frequent, a period of only ten to twelve hours intervening. In some cases the temperature chart can not be distinguished from that of typhoid; in other cases, the fever is that of malaria. A number of recorded cases have been confused with the above diseases or with paratyphoid fever but the Widal proved negative or parasites could not be found in the blood, and a correct diagnosis was finally reached by a positive blood culture. The pulse is in proportion to the temperature during the early stages of the disease but later becomes weak and thready and may remain at 130 to 140 even while the temperature is normal. The respirations follow the temperature and pulse quite closely except when pulmonary complications develop.

In place of the mental apathy or semicoma or alternating with it may be a mild delirium. Occasionally mental clearness persists throughout the disease. The profound toxemia is evidenced not only by the mental changes, chills and high temperature, but by the severe prostration, septic facies and rapid emaciation. Hemorrhages are rather common, either from the intestines, kidneys or uterus. Rochester reported a case in which a fatal hemorrhage occurred from the gums.

Cutaneous lesions are rare. Herpes is probably the most common and is similar to that seen in many toxic conditions. Occasionally an elevated, blotchy eruption covers the entire body or petechial hemorrhages or rose spots similar to those of typhoid fever are noted. Jaundice is quite common especially in the cases with abscess in the liver. A brownish pigmentation of the skin of the entire body has been noted in a number of instances and seems to be of diagnostic importance when present. It may be so marked as to give the color of a very dark Indian. The sclera is yellowish or brownish yellow.

Metastatic infections are rather common although not as frequent as in the staphylococcus septicemias. They may occur in any part of the body and often entirely change the clinical picture. At times, metastatic abscesses are practically the only evidence that a septicemia is or has been present.

The physical examination is usually negative except for the freqeunt occurrence of an enlarged spleen. In a certain number of cases the liver is likewise enlarged. This is usually associated with jaundice and may be due either to the toxic conditions or to liver abscess. A few cases have been reported in which swelling and tenderness of the joints suggested acute articular rheumatism. Metastatic abscesses may or may not be demonstrable, depending upon both their location and their size.

The laboratory findings are important and are frequently the only means by which a correct diagnosis can be made.

The blood shows a secondary anemia, average counts early in the disease running from 2,700,000 to 3,000,000. In the later stages the count may drop to 2,000.000 per cu. mm. The hemoglobin averages 45 to 48 per cent. A leukocytosis is usually present, especially in the cases with metastatic abscesses. Here the white count varies from 30,000, to 40,000 per cu. mm. and has been reported as high as 79,200 per cu. mm.

The differential count shows 78 to 98 per cent. polymorphonuclear leukocytes, 5 to 8 per cent. large lymphocytes, 2 to 3 per cent. small lymphocytes, 2 per cent. eosinophiles, 4 per cent. transitionals, and 0.5 to 1 per cent. nucleated red cells. In the cases resembling typhoid fever, a definite leukopenia may exist, the white count dropping to 5,000 per cu. mm.

Blood cultures show an abundant growth of the colon bacillus. Examination of the blood both before death and at autopsy has occasionally shown methemoglobin.

The urine may be normal throughout the disease but usually shows some albumin. Microscopic blood is a frequent finding and many cases have considerable quantities of blood in the urine. A colon bacillus pyelonephritis is common and large quantities of pus are then present. The organism is almost always demonstrable in the urine.

Cultures of the pus from metastatic abscess will show large numbers of the bacillus coli. As a rule, the pus is thick, yellowish in color and has a typical colon odor.

Diagnosis.—Recognition of this particular form of septicemia is often difficult, especially in the type resembling typhoid or paratyphoid fever. Differential diagnosis will depend upon a negative Widal test and primarily upon the blood culture. The type with multiple abscesses is more easily recognized, at least the presence of a septicemia is evident and a positive blood culture will determine the infecting organism.

The symptoms and physical findings are not sufficient in themselves to entirely exclude staphylococcus or streptococcus septicemia. Cutaneous eruptions are less common in colon bacillus infections and their presence would tend to exclude the organism as the causative agent.

Complications and Sequelæ.—Pneumonia, usually of the bronchial type, is the most common complication arising duing the course of the disease. Frequently it is a terminal infection and may be only evident at autopsy. Sequelæ are rare with the exception of chronic pyelonephritis.

Colon bacillus septicemia is often associated with septicemia due to other organisms. The most common are the staphylococcus and streptococcus, atlhough bacillus pyocyaneus, micrococcus tetragenous and the pneumococcus have been found. It occurs as a terminal infection in a large number of diseases but particularly those of the genito-urinary tract.

Three types are often described. These have already been mentioned as the type resembling typhoid, the type with metastatic abscesses, and the type which appears as a terminal infection. To this should be added a fourth type known as Winkel's disease which is a rapidly fatal disease of the new-born.

Treatment.—Very little can be done from the prophylactic standpoint. The early recognition of acute appendicitis and modern surgical treatment will reduce to a certain extent the cases of general sepsis arising from this focus. So also will the two stage operation for prostatectomy, since in the one stage the opportunities for the spread of the colon bacillus seem much greater. The treatment is largely symptomatic. A **careful diet, absolute rest, temperature baths** when the fever reaches high levels, and **careful nursing** constitute our entire established therapeusis. **Vaccines** have been recommended by various authors with diametrically opposing results. Much was hoped for vaccine therapy in its early days, but at present the vaccines for colon bacillus are on definite trial with the evidence about equally divided as to their therapeutic value. The dose usually consists of five hundred million rapidly increasing at three to five day intervals until one thousand million or more are given. The surgical treatment consists purely in the drainage of secondary abscesses. Convalescence may be long drawn out. At this period **hexamethylenamin,** grains x in a full glass of water three or four times a day, apparently helps in overcoming the colon bacillus pyelonephritis. **Fluids** should be given in abundance throughout the course of the disease.

Prognosis.—Death is usually due to the intoxication or to a terminal bronchial pneumonia. Occasionally death is due to meningitis, brain abscess or hemorrhage. The mortality varies with the source of the original infection. When from the urinary tract, the prognosis is comparatively good. When from appendicitis or cholecystitis, the outlook is extremely unfavorable. The average mortality is about 50 per cent. In the cases of septicemia in children, the mortality is practically 100 per cent.

Pathology.—The macroscopic findings at autopsy are: emaciation, sometimes deep bronzing of the skin and a deep yellow color to the sclera; deep yellow color in subcutaneous fat; abscesses in the brain; purulent meningitis; empyema of thoracic cavity; multiple abscesses in lung; bronchial pneumonia; abscesses in heart muscle; intima of aorta and endocardium covering valves may show deep chocolate color; fatty degeneration of liver; multiple abscesses of liver; generalized purulent peritonitis; enormous swelling of spleen; multiple abscesses of spleen; cloudy swelling of kidney; multiple abscesses of kidney; purulent exudate in uterus; multiple abscesses in prostate; occasionally a deep bronze color of the intestine, and a dark chocolate color to the mucosa of the bladder.

Microscopical findings, in addition to the gross findings above, are: cloudy swelling and fatty degeneration of heart muscle; edema of lungs with infiltration of polymorphonuclear leukocytes and lymphocytes, atelectasis, and considerable exfoliation of epithelial cells filling alveolar spaces; cloudy swelling and fatty degeneration of the liver with local collections of organisms and infiltration of leukocytes. Spleen: great increase of lymphoid and plasma cells, areas of necrosis infiltration of leukocytes and collections of organisms. Kidneys: cloudy swelling, tubules and Bowman's capsule distended with chocolate colored serum showing reaction of hemosiderin. Examination of the blood which was deep chocolate in color in some cases showed the spectrum of of methemoglobin.

BACILLUS PYOCYANEUS SEPTICEMIA

Definition.—Bacillus pyocyaneus septicemia is a generalized blood borne infection, due to the entrance into and multiplication within the body of the bacillus pyocaneus. ,

Etiology.—Predisposing Causes.—Little is known of the predisposing factors in the infection. The general causes of lowered resistance to any infection, such as exposure to cold, poor food, or a previous illness, are undoubtedly active here, but no single or group of predisposing causes has been found to have any special importance.

The sex apparently has no significane, but age is an important factor. In the acute form of this disease all ages, with the possible exception of these considerably past middle life, seem equally susceptible. In the chronic form, however, the majority occur in infants or children.

So far as known there is no particular individual susceptibility nor have we any evidence as to individual immunity, either natural or acquired. However, it is possible that a certain degree of immunity is developed as we know of no case which, having once completely recovered from this infection, was again ill with the same disease. Animal experimentation suggests the development of some immunity.

Bacteriology.—The bacillus pyocaneus is an actively motile, short rod measuring one to two microns in length by three tenths microns in thickness, and has definitely rounded ends. It is either straight or slightly curved, usually the former, occurs singly or occasionally in short chain of two or three. The motility is due to a single flagellum at one end. It is Gram negative, stains readily with the usual dyes, and is easily cultivated on ordinary media. It produces in the presence of oxygen a greenish pigment named pyocyanin. On agar slants the pigment is noted in eighteen to twenty-four hours. It is this pigment which gives the characteristic color to the outer layer of infected dressings and has given the organism the name of bacillus of blue or green pus.

Distribution.—The organism is apparently a rather common skin contamination, but because of its rather low virulence, serious infection is comparatively rare. It may be found in the nose and throat of healthy individuals. Associated with other organisms it is frequently found in dirty, uncared-for wounds, in fact it is most often seen in mixed infection or as a secondary invader. It is frequently found in the feces, both of healthy individuals and of those with diarrheal and dysenteric discharges. In cases of septicemia the distribution within the body is very extensive, there being practically no organ or tissue which has not been found involved.

Modes of Conveyance.—The organism is probably carried largely by direct contact, but being so widely distributed it is reasonable to assume that the great majority of the infections are from bacteria already present in the patient's body. The organism may be easily spread by contaminated instruments or dressings and is probably carried by flies.

Infection through healthy, unbroken skin or mucous membrane is unknown. Abrasions and especially ragged, deep wounds with considerable devitalized tissue offer excellent foci for infection. The method of invasion in septicemia cases is doubtful. The infection in even the most extensive wounds usually remains well localized and Welch states that no instance of invasion of the body from wounds had been noted by him. However, nothing is known of the incubation period and it seems very possible that because of its low virulence the organism may enter through a wound and remain for an indefinite period after the original focus has healed before symptoms of a generalized infection develop.

There is considerable evidence that the organism may gain entrance to the body through the usual portals of entry as the ear, nasal cavities, mouth, particularly abscessed teeth, tonsils, and ulcers or other lesions in the gastro-intestinal tract.

The bacillus undoubtedly spreads widely by way of the blood stream, but there is no positive evidence that it actually multiplies in the circulating blood as does the streptococcus. The development of new foci in the body is usually due to lodgement of infected emboli.

Types of Infection.—There are two types of severe bacillus pyocyaneus septicemia, acute and chronic. Occasionally light infections have been noted and there are probably other cases which have not been recognized. The acute, fulminating type is the usual form and lasts for only a few days. The chronic type is decidelly rare, occurs chiefly in infants or young children, although adult cases have been reported and may persist from a few weeks to several months.

The acute systemic infection with bacillus pyocaneus is characterized by the sudden onset of high fever of the septicopyemic type, violent pains in the head, back and limbs, and nausea with severe vomiting and diarrhea. An erythematous eruption, confined largely to the trunk and extremities, appears in a few hours. This cutaneous manifestation of sytemic infection appears as moderate sized reddish or bluish macules and papules or as small vesicles, pustules or even hemorrhagic petechiæ. Hemorrhagic and necrotic enteritis is common. Death usually takes place in a few days.

The chronic systemic infection with bacillus pyocyaneus generally begins acutely with the symptoms of a severe gastro-intestinal disturbance. A severe chill frequently precedes the violent vomiting, purging, excruciating headache, backache, and rapidly developing hyperpyrexia with which the patient suffers the first twenty-four hours. For the next day or two immediate recovery seems evident, the gastro-intestinal symptoms disappear and the temperature returns to normal. The fever then returns with daily exacerbations and remissions which occur at irregular intervals. The temperature always rises rapidly to 102° to 104° F. (38.8° to 40° C.) remains at the high point about half an hour and then suddenly drops to subnormal, sometimes as low as 94° F. (34.4° C.). The fever is accompanied by severe chills and the sudden drop in temperature is preceded by a profuse sweat. Headache is present during the periods of pyrexia. Backache and extreme neuralgic pains in the lower extremities are common. Constipation usually follows the initial diarrhea.

Cutaneous lesions develop within a few days. At first they appear as an erythema multiforma—a reddish or bluish maculo-papular eruption developing over the extremities but to a less extent on the trunk. The face may escape. Later nodules as in erythema nodosum may appear in the same regions and even on the palms of the hands and soles of the feet. The nodules are tender and vary in size up to two centimeters in diameter. Vesicles and pustules may appear, but are uncommon. The eruption develops rapidly, then slowly fades, and may entirely disappear before a new one appears. These cutaneous lesions develop at irregular intervals, but tend to become less severe and may finally cease after several weeks or months even though the temperature shows that an active process still exists.

The pains in the back and legs are frequently more violent just preceding the reappearance of a cutaneous eruption. They may last for several months, varying greatly in severity and are typically neuralgic in character.

A slowly developing paresis of the lower extremities, accompanied by more or less marked atrophy of the limb muscles has been described. This muscular weakness may persist after the patient has otherwise recovered, but gradual improvement usually takes place. Sensation in the lower extremities may be lost.

The spleen is nearly always enlarged and the liver frequently. Cirrhosis of the liver, occasionally with jaundice, is not uncommon, but probably plays a small part in the production of the ascites which has been noted in several cases. The collection of serous fluid in the pleural and peritoneal cavities may clear up after a single aspiration or may become purulent. Hemorrhages from the intestine are common, frequently severe and sometimes fatal. The blood may appear fresh in lesions of the rectum, colon and lower ileum, or appear in the form of tarry stools from lesions higher up in the small intestine. Meteorism is a frequent accompaniment.

The following lesions presumably due to the bacillus pyocyaneus have been noted clinically during the course of the disease: meningitis; purulent bronchitis; bronchopneumonia; acute and chronic nephritis; pyelonephritis; purulent cystitis; paralysis of bladder musculature; acute and chronic cholecystitis; acute hemorrhagic enteritis; intestinal paralysis; acute colitis; gangrene of skin and subcutaneous tissue; serous effusion into the peritoneal, pleural, pericardial, and joint cavities;

purulent peritonitis; paralysis and atrophy of leg muscles; and various types of skin eruptions including macules, papules, vesicles, pustules, hemorrhagic petechiæ and grosser lesions as erythema mulitforme or erythema nodosum and even extensive skin lesions resembling acute exfoliative dermatitis.

Physical Findings.—As is evident by the foregoing list, the lesions which may be found on physical examination are very diversified, and will depend entirely on what structures are involved in each case. However, the signs observed will not differ specifically from those seen in any pyogenic involvement of the organs or tissues under consideration. For example, the meningitis due to pyocyaneous infection will present the usual rigidity of the neck with the head drawn backward, exaggeration of the reflexes early in the disease, Kernig's sign, frequently the Babinski phenomenon, and often twitchings or even convulsions. Paralysis of one or both external recti muscles is a common finding. The purulent bronchitis, or bronchopneumonia will present the usual purulent sputum, often blood streaked, and on percussion and auscultation the typical areas of dulness and bronchial breathing with numerous rales will be heard. The same may be said for the effusions into the various serous cavities, the purulent peritontis and pleuritis, and the acute and chronic cholecystitis.

The only characteristic physical finding, and the one for which repeated examinations should be made, is the typical cutaneous eruption. The absence of a positive blood culture may be only the means of arriving at a correct diagnosis.

The other physical findings are of importance only as indicating the presence of some form of septicemia, an extension of complication of the disease or the prognosis.

Laboratory Examinations.—The blood picture is not characteristic. A moderate leukocytosis of 12,000 to 15,000 with an increase of the polymorphonuclear neutrophilic leukocytes up to 95 per cent. may be present. More often the white count is normal or an actual leukopenia exists. The erythrocytes are decreased in number, but moderately as a rule. The hemoglobin shows a slight anemia. No changes in the red cells are noted in the acute cases, in the chronic infections the changes characteristic of secondary anemia are usually found. The bacillus pyocyaneus will usually be obtained, at least after repeated blood cultures are taken.

The urine may be normal, or show a slight increase in specific gravity, some albumin and at times casts. In the severe hemorrhagic cases red blood cells may be found. When acute nephritis develops the urine will be scanty, highly colored, of high specific gravity and frequently contains large amounts of albumen and casts.

In the presence of pyelitis or pyelonephritis, many pus cells will be noted. The bacillus pyocyaneus has been frequently found in the urine. The appearance of the organism in the hanging drop or stained smear is suggestive but the diagnosis should only be made by culture after a specimen has been obtained under sterile precaution. In the female this necessitates catheterization.

The feces may be normal either throughout the illness or during the intervals between attacks of diarrhea, although acute enteritis occurs with great frequency. Nothing characteristic has been regularly noted concerning the diarrhea stools. Fresh blood from ulceration of the colon is a rather common finding and more or less changed blood from hemorrhages in the small intestine may be expected. Occasionally the feces are greenish and have a very peculiar offensive odor. A so-called fetid diarrhea has been noted in many of the reported cases. The bacillus pyocyaneus is frequently found in the feces, sometimes in large numbers. Inasmuch as the organism is often found in stools of healthy individuals, its presence, except in large numbers or unless found constantly in several individuals suffering simultaneously from a severe enteritis, can scarcely be considered diagnostic. Sartigan during an epidemic of an acute enteritis resembling dysentery found this organism constantly present in the feces and traced the infection to the drinking water in which he found the bacilli abundant.

Examination by both cultural and staining methods should be made of all transudates and exudates since the bacillus has been found in the vesicles of cutaneous eruptions, in the discharge from the ear in case of otitis media and in the pus from abscesses of diverse distribution and without relation to possible air contamination, such as fistula in ano, chronic mastitis, ovarian abscesses, pericardial empyema and prepatellar bursitis.

Diagnosis and Symptomatology.—This can be made definitely only by the finding of the bacillus pyocyaneus in the blood or in the numerous lesions which may develop.

In the acute or fulminating type, the clinical history of sudden onset, the septicopyemic temperature, violent pains, vomiting, and diarrhea, associated with an erythematous eruption, especially of reddish or bluish macules and papules confined largely to the trunk and extremities, is very suggestive of an acute bacillus pyocyaneus septicemia. Repeated blood cultures should be taken as the organism will not be found constantly, at least in the peripheral blood stream. Cultures of the urine may give positive findings when blood cultures have failed. The presence of the bacillus in the stools, while highly suggestive, is always open to question and we do not believe that this single finding in the absence of other more or less conclusive data, should be considered sufficient evidence on which to make a definite decision. Death usually takes place before emoblic abscesses appear, but should they be present, culture from them will prove the diagnosis as may cultures from the cutaneous lesions.

The diagnosis of the chronic type is often more difficult since the majority of the cases occur in young children in whom the typical symptoms may not be sharply defined. Even in the adult the condition may not be recognized, largely no doubt, because the symptoms of certain common diseases are so pronounced as to over-shadow the indications of a generalized infection. Bronchopneumonia with subsequent empyema, pyelonephritis, and cholecystitis are typical examples, and in such cases the characteristic skin eruption and pain are either not pronounced, absent or their significance is unrecognized.

The typical symptoms, however, especially in the adult, are so characteristic that a tentative diagnosis may be made even before the recovery of the organism from the blood, urine, or pus from some focus of infection. The severe gastro-intestinal disturbance, manifested by violent vomiting and purging, frequently preceded or initiated by a severe chill, and accompanied by a high fever, prostration, excruciating headache, backache and sometimes pain in the limbs is very suggestive, but a similar symptom complex occurs in the early stages of some other diseases, notably the acute exanthemata.

The apparent rapid improvement after the first twenty-four to forty-eight hours, lasting two or three days, followed by a return of the original symptoms, although not necessarily in their initial severity, suggests at once a generalized infection presumably due to the bacillus pyocyaneus. The gastro-intestinal symptoms may be absent, but there is usually a daily rise in temperature, the fluctuation occurring at irregular intervals, being particularly impressive because of their great latitude and frequently by the severity of the accompanying chills. The especially noteworthy features of this disease may not develop until a number of days later. Then are found the numerous cutaneous lesions varying from a reddish or bluish maculopapular eruption to vesicles, pustules, and nodules resembling those in erythema nodosum. The appearance of these cutaneous lesions is particularly significant. The association of neuralgic pains with a recurrent cutaneous eruption and at times the development of marked weakness or even paralysis of the extremities is of great diagnostic interest. At times the correct diagnosis will be made or at least definitely confirmed only when some of the various complications arise, such as acute cholecystitis, necessitating an operation, at which time the bacteriological examination of purulent material will disclose the bacillus pyocyaneus. Barker described this disease as a "generalized hemorrhagic septicemia accompanied by a vesicular skin eruption, yielding a clinical picture not unlike typhoid fever."

The symptoms of the atypical case may strongly suggest some other type of disease, such as meningitis, typhoid fever, catarrhal jaundice or pneumonia. The initial complaint may be headache, drowsiness and vomiting as in a case described by Clark. Diarrhea may be entirely absent and replaced by obstinate constipation. The violent chills may not appear until late in the disease and the temperature may remain only moderately elevated until the septicemia is well advanced. Severe jaundice may be present with marked enlargement of the liver. Cough and pain in the chest, together with weakness may be the chief complaint and suggest a pleurisy or pneumonia. The characteristic skin lesions may be absent at all times, especially in the acute fulminating type.

The physical findings of diagnostic significance are largely confined to the cutaneous lesions. The data elicited by the routine methods of physical examination during the development and course of the many complications differ in no way from the findings in the more common pyogenic processes.

Main reliance must be placed on the laboratory examinations, particularly the repeated taking of blood cultures. The presence of the organism in pure cultures from the cutaneous lesions, from the urine, or from foci of infection in outer parts of the body, is of practically equal importance to a positive blood culture. The presence in great abundance of the organism if found in the water or milk supply indicates a pyocyaneus enteritis and the probability of a pyocyaneus septicemia.

Complications.—As pointed out in a previous paragraph, practically every tissue in the body may be directly invaded by this organism. Meningitis is fortunately rare and probably occurs most frequently by direct extension from an original focus in the middle ear. Purulent bronchitis, bronchopneumonia, and empyema are more often a terminal infection, especially associated with some wasting disease and may in fact precede rather than follow the pyocaneus septicemia. Acute nephritis is commonly found in the more severe cases and is probably a result of the toxemia, while pyelonephritis, which has been noted many times, is due either to the lodgment of an infected embolus or to the multiplication within the renal tissues of single organisms which have entered from the blood stream. Purulent cystitis may be secondary to the pyelonephritis and has been found in the majority of cases coming to autopsy. Acute and chronic cholecystitis may be either a complication of the septicemia or be the original focus from which the generalized infection spreads, and certainly in one reported case the gallbladder was evidently the reservoir from which repeatedly invasion of the blood stream took place. It seems, therefore, particularly important from the standpoint of treatment that the presence of either an acute or chronic cholecystitis should be recognized.

A severe enteritis, sometimes hemorrhagic in character, is a grave complication, as the nutrition of the patient is seriously interfered with. The intestinal hemorrhages may lead to a pronounced, even alarming, acute anemia and in a few cases have evidently been so severe as to be the immediate cause of death.

Serous effusions into the peritoneal, pleural, pericardiac and joint cavities are not necessarily serious and if slight or moderate in amount may cause very few symptoms. However, they may become purulent and change the whole aspect of the case. Purulent peritonitis has been particularly fatal. It may arise either from a primary serous effusion in the abdominal cavity or from some particular focus such as an appendiceal abscess, cholecystitis, or mesenteric adenitis. Abscesses may develop in any organ or tissue of the body.

Sequelæ.—Since the vast majority of reported cases have died from the septicemia or its complications, very little has been recorded concerning the possible sequelæ. It is known that the paralysis and atrophy of the extremities may be entirely overcome, but some weakness at least usually remains and a more or less noticeable atrophy will persist, depending largely upon the severity and duration of the initial paralysis.

Chronic adhesive pericarditis and pleuritis would be expected in a certain proportion of those who recover. Also peritoneal adhesions would be expected. Suppuration in the joint cavities would give more or less impairment of function, depending upon the extent of the destructive process.

Chronic nephritis will be found in a small percentage of cases, the result either of the long continued toxemia or of a pyelonephritis.

Association with Other Diseases.—In an adult, described by Brill, a bacillus pyocyaneus septicemia developed just as the patient was apparently recovering from a staphylococcus aureus septicemia, and Finkelstein found both pyocyaneus and colon bacillus septicemia in a child of three months. It has also been found associated, probably as a terminal infection, in cases of chronic nephritis, advanced pulmonary tuberculosis, diabetes, and carcinoma of various organs.

Clinical Varieties.—There are two types of bacillus pyocyaneus septicemia; an acute and a chronic form. Occasionally intermediate forms will be found.

Treatment.—Of first importance is the **detection and elimination** of the **primary focus** of infection and of any **secondary foci** which may develop. The importance of the latter in continuing the infection is well illustrated by a case reported by Freeman. Here the primary focus could not be determined although it may have been in alveolar abscesses which were discovered by the x-ray. Removal of the diseased teeth and treatment of the abscesses did not improve the patient's condition, and not until symptoms of cholecystitis developed, resulting in drainage of the gall-bladder, recovery of the bacillus pyocyaneus from the bile, and the administration of an autogenous vaccine, did improvement set in. The cholecystotomy may have favorably influenced the course of the disease, but Freeman apparently considered the **vaccine** as the most important of the therapeutic measures. The **autogenous vaccine** was given at intervals of five days commencing with 800,000 bacteria and increasing the same amount each succeeding injection until 8,000,000 were given at each period. The vaccine was then continued at this dosage until the symptoms of the disease had largely disappeared.

This vaccine treatment has been advocated by a number of authors and for the chronic septicemia is probably the most efficient therapeutic measure at the physician's disposal. The disease is so rapidly fatal in the acute cases that the vaccine probably will be found of little or no value. Certainly it would have to be given very early and in comparatively large amounts. It is possible a protective vaccine might be of benefit as a prophylactic measure in cases of localized pyocyaneus infection. Animal experiments showed some immunity could be developed by repeated inocculations of the bacillus and an antipyocyaneus serum might be developed which would be of real value in the treatment of the fulminating cases. Bouchard made such an antipyocyanic serum four years before Behring developed the diphtheria anti-toxin. However, the comparative rarity of the cases which are recognized before death, would not warrant the production of such a serum on a commercial basis.

The general condition of the patient must be kept up, preferably by **rest, good food,** and **fresh air.** The **diet,** except when acute enteritis is present, should be **simple** but **adequate,** and special dishes and care in serving will do much to overcome the anorexia which seems a common complaint of the chronic case. During the period of acute emesis and diarrhea, food of any kind may not be tolerated. **Buttermilk** may often be taken when all other foods are promptly vomited. Large numbers of calories can often be introduced through the use of **milk sugar** to sweeten lemonade, orangeade or other fruit juices, since a much larger quantity is required than with cane sugar. **Water** in large amounts should be consumed and if it cannot be taken by mouth, should be introduced **by rectum** or in diarrhea cases, by **subcutaneous infusions** of **salt solution.**

Blood transfusion is definitely indicated if severe hemorrhage takes place from the gastro-intestinal tract, and should be repeated as often as seems necessary. The use of blood in cases of septicemia purely as a therapeutic measure, that is, in the absence of hemorrhage, is still a debated question. It is quite certain, however, that blood transfusion is of great value to combat the secondary anemia, and can be used with comparative safety after the active process has subsided.

The severe neuralgic pains in the back and lower extremities can be relieved to a certain extent by **acetyl salicylate, grains X (0.6 gram)**, every four or six hours as the symptoms indicate. The severe headaches may be somewhat relieved by the salicylate, but usually require a more drastic drug. **Acetphenetidin, grains V (0.3 gram)**, may be used, but **codein, grain ½ to 1** (0.03 to 0.06 **gram**), by hypodermic injection or a slightly larger dose by mouth is probably safer.

Atrophy of the extremities can be largely prevented or at least, rendered less severe, by **proper massage.** Contractures can and should be prevented by the application of **suitable splints** or **traction.** It is questionable if any benefit accrues from the use of electricity for the paralysis.

The surgical indications are those required for the removal of the initial focus of infection and the treatment of secondary foci. Since the complications which may arise are numerous, it would be useless to take up in detail the surgical procedures which may be required. Suffice it to say that the routine surgical measures for the treatment of pyogenic infection in general apply equally well to the treatment of abscesses arising from this particular organism.

Prognosis.—In the acute case, the prognosis is very grave, death usually taking place in three or four days. The disease may last for two or three weeks but even then is nearly always fatal.

The prognosis of the chronic type is much better, a number of reported cases surviving. The convalescence may be prolonged for months, but ultimate recovery with little or no residual effects may be expected in at least 25 per cent. A certain amount of deformity due to paralysis and atrophy of the muscles of the extremities may be permanent. Other permanent impairments of function will depend upon the complication, their extent and duration.

Pathology.—The following lesions produced by the bacillus pyocyaneus and from the majority of which the organism has been recovered, have been found at autopsy: Purulent meningitis; purulent otitis media; empyema of maxillary, frontal and sphenoidal sinuses; ulceration with hemorrhage and necrosis of esophagus; ulceration and hemorrhagic necrosis of stomach: necrosis with superficial and deep ulcers throughout entire small intestine, ascending, transverse and descending colon and rectum; perforated ulcers in ileum and rectum; acute hemorrhagic enteritis without ulceration; paralysis of small intestine; acute colitis, suppuration of mesenteric lymph glands; hepatic abscess; ovarian abscess; acute purulent peritonitis; acute nephritis; pyelonephritis; hemorrhagic and necrotic cystitis and ureteritis; paralysis of musculature of urinary bladder; purulent bronchitis; bronchopneumonia; empyema; pleurisy with organized exudate; hemorrhages into and paralysis of smooth muscles of bronchi; purulent pericarditis; endocarditis with vegetations on mitral valves; hemorrhagic infarcts in lungs, kidneys, spleen and intestine; hemorrhage and thrombosis in cutaneous tissues; fatty degeneration of heart, liver and kidneys; purulent synovitis; suppurative phlegmon in muscles and subcutaneous tissues; vesicular eruption; acute exfoliative processes in skin and mucous membranes; gangrene of cutaneous and subcutaneous tissues; acute and chronic cholecystitis; empyema of gall-bladder; cholelithiasis with recovery of the bacillus pyocyaneus from the interior of the gall-stones.

The microscopic findings reported from autopsies are fatty degeneration of the heart, pyopericarditis, vegetations on the heart valves, plugging of capillaries in various parts of the body by the bacillus, edema and passive congestion, and acute inflammation extending to suppuration in lymph glands.

No findings in the respiratory system other than those noted in the macroscopical report have been recorded. The spleen has shown parenchymatous degeneration and necrosis, numerous areas of hemorrhage, thickening of the capsule, increase of the connective tissue, a yellowish-brown pigmentation, and large numbers of bacilli scattered throughout the organ. The liver showed intense, acute parenchymatous degeneration with areas of necrosis, increase in connective tissue, marked infiltration of round cells, and dilatation of the vessels, in the walls of which, as well as plugging the capillaries, were myriads of bacilli.

The intestine showed infiltration with both mononuclear and polynuclear leukocytes. Areas of necrosis varied from simple ulcers in the mucosa to complete necrosis and perforation of all walls. Many hemorrhages due to the rupture of the capillaries were found.

The kidneys showed parenchymatous degeneration, small abscesses containing bacilli, and edema, granular degeneration and desquammation of the cells of the tubules. Some organisms appeared throughout the intestinal tissue. The adrenals showed marked acute degeneration with vacuolization, the process being most pronounced in the medulla.

Historical Summary.—Infections with the bacillus pyocyaneus have been known since the earliest days of medical history, as many old references can be found describing the greenish or bluish pus which is so charateristic. The first case of pyocyaneus septicemia diagnosed by blood culture was that of a three month's old child reported by Finkelstein in 1899. Since then, many more cases have been reported, but the majority have not been recognized except at the autopsy table.

SEPTICEMIA DUE TO THE BACILLUS MUCOSUS CAPSULATUS, TO THE MICROCOCCUS TETRAGENOUS, TO THE MENINGOCOCCUS, TO THE PNEUMOCOCCUS, AND TO THE GONOCOCCUS

The septicemias due to these organisms are of rare occurrence and so will be given in very brief form.

BACILLUS MUCOSUS CAPSULATUS SEPTICEMIA

This disease starts with generalized pain, especially in the larger joints, and a sudden rise in temperature to 101° or 102° F. (38.3° to 38.8° C.). Purpuric spots occur over the entire body, especially over the lower extremities. There may be marked swelling in the various joints which has a tendency to disappear from one and reappear in another. The white count is generally increased, an average being 24,500. This infection more often develops from otitis media than from any other focus. The mortality is high.

MICROCOCCUS TETRAGENOUS SEPTICEMIA

This infection develops most commonly in those debilitated by some previous infection. It is somewhat contagious as there is evidence that it develops more frequently in orderlies and nurses taking care of patients infected with this organism than in people not so exposed. The disease may not be distinguishable from paratyphoid and it has been suggested that many of the cases of so-called trench fever are a tetragenous septicemia. The onset may be sudden or insidious. Headache and pains in the lower back and from the knees to the ankles with sometimes extreme tenderness over the tibia is quite characteristic. The spleen may be enlarged and rose spots resembling those of typhoid fever are occasionally noted. The patient is usually lethargic. Some cases show only a slight headache and slight fever for three to four weeks before the development of more severe symptoms. Death may take place in five days to eight weeks. The white count is usually low and the anemia only slight. Prognosis is good. Treatment consists in the use of vaccines.

MENINGOCOCCUS SEPTICEMIA

This disease develops with a sudden onset, being characterized by the rapid development of a severe intoxication. The first symptoms are chilliness and malaise. Within eighteen hours a profuse hemorrhagic purpura may cover the entire body and death may take place in twenty hours from the initial symptom. The white count is usually only slightly increased and the polymorphonuclears remain normal in number. There appears to be an increase in the enucleated reds. The patients who live for several days frequently show swelling and have pain in the hands, elbows and knees, with chills followed by fever. There also may be petechial spots on the ocular and palpebral conjunctiva. Occasionally, rose spots as in typhoid appear in consecutive crops. The petechial hemorrhages over the abdomen may coalesce to form irregular blotches, varying from a pinhead to 2 cm. in diameter. They are purple when first seen and generally change to a reddish purple. They are frequently elevated irregular in outline, and sometimes are very tender. The petechial spots on the pharynx change to a whitish color and may become necrotic. The mortality is very high. If the case is recognized early and anti-meningococcus serum given, the death rate would undoubtedly be materially reduced. Meningitis may or may not be associated with the septicemia. One case was reported in which the organism was found in the meninges of the mother and of her seven months fœtus.

PNEUMOCOCCUS SEPTICEMIA

This type of septicemia is especially common with lobar pneumonia and, in fact, many consider all cases of lobar pneumonia as having a septicemia at some period. The temperature is high, running to 104° to 105° F. (40° to 40.5° C.) with a pulse of from 112 to 140, and respirations varying from 28 to 48. The initial symptoms are not clear cut; occasionally a severe chill ushers in the infection. At other times, severe cramp-like pains in the abdomen are the first complaint. The patients are nervous, very irritable and frequently delirious. The pneumococcus septicemias without pneumonia have a rather high mortality, some dying with four days. No treatment has been found that is efficacious.

GONOCOCCUS SEPTICEMIA

Gonococcus septicemia is characterized by joint involvement and endocarditis. The leukocytosis varies from 9,400 to 19,000, the latter being found most frequently in the presence of vegetative growths on the heart valves. As a rule, only one joint is involved, but at times all the major joints may be affected. Meningitis has been reported occasionally and is the most fatal complication. The treatment has generally consisted of the use of vaccines and the majority of reports are favorable to its use. However, some authors have reported no improvement whatever from using both stock and autogenous preparations. Except with meningeal involvement, there is practically no mortality.

BIBLIOGRAPHY

Septicemia in General

Anderson, H. M., and Richardson, C. Septicemia as a complication of gunshot wounds with notes on 13 cases. Brit. Jour. Surg., 1917–18, v, 393.

Berghausen, O. The diagnosis and treatment of septicemia. Interstate Med. Jour., 1916, xxiii, 799.

Brown, W. H. A clinical study of some pyogenic lesions observed in France. Brit. Jour. Dermat. and Syph., 1917, xxix, 241.

Burnham, A. C. Serum therapy in septicemia. Ann. Surg., 1914, lix, 652.

Churchman, J. W. Cutaneous manifestations of septicemia. Amer. Jour. Med. Sci., 1913, cxlxi, 833.

Duval, C. W., and Lewis, P. A. General septicemia. Jour. Med. Research, 1905, xiii, 535.

Henderson, J. Septicemia with local endocardial lesions with record of 9 cases. Lancet, 1912, 11, 745.

Herrick, W. W., and Warren, M. Bacteriemia. Med. and Surg. Report, Roosevelt Hosp., New York, 1915, 223.

Hicks, J. A. Braxton. An Account of a bacillus of an unusual kind isolated from a case of septicemia. Proc. Roy. Soc. Med., 1912–13, vi, 133.

Steel, W. A. Treatment of pyemia and septicemia by transfusion of immunized blood. Inter. Clinics, 1917, iv, 275.

Symmers, D. Anthrax septicemia. Ann. Surg., 1922, lxxv, 663.

Tumpeer, Harrison and Grevinson, A. Fatal infections following tonsillectomy. Jour. Amer. Med. Assoc., 1923, lxxx, 20.

Warren, Mortimer and Herrick, W. W. Analysis of 134 cases of bacteriemia. Amer. Jour. Med. Sci., 1916, cli, 556.

Western, G. T. The treatment of some septicemias by vaccines. The Practitioner, London, 1915, xciv, 724.

Streptococcus Septicemia

Brown, E. D. The relationship between puerperal septicemia and other infectious diseases with reference to the admission of maternity cases into isolation hospitals. Proc. Roy. Soc. Med., London, 1922, xv, 49.

Bryan, C. W. G. Pyemia treated with antistreptococcus serum. Lancet, 1922, 1500.

Burnham, A. C. Vaccine and serum therapy in septicemia. Ann. of Surg., 1914, lix, 652.

Ehrenfest, H. The prophylaxis and treatment of puerperal infection. Ann. Jour. Obstet. and Gynec., 1920, 1, 108.

Gow, A. E. Intravenous protein therapy in puerperal septicemia. Brit. Med. Jour., 1920, ii, 268.

Murray, H. L. Sera and vaccines in the treatment of puerperal infection. Brit. Med. Jour., 1920, ii, 269.

Titus, R. S. Puerperal sepsis and its treatment. Bos. Med. and Surg. Jour., 1920, clxxxiii, 871.

Watlon and Medalia. Hemolytic streptococcus and puerperal septicemia. Surg. Gynec. and Obstet., 1912, xv, 682.

Western, T. The treatment of puerperal sepsis by bacterial vaccines. Lancet, 1921, i, 351.

Staphylococcus Septicemia

Blumer, G. Report of a case of rapidly fatal septicemia due to the staphylococcus albus. Yale Med. Jour., 1910, xvi, 265.

Carter, Willia and Wesley. A case of staphylococcemia. Laryngoscope, 1917, xxvii, 579.

Coffey, W. B., Carson, G. R., and Cummins, W. F. An unusual case of septicemia. N. Y. Med. Jour., 1913, xcviii, 377.

Farnell, E. J., and Harrington, A. H. Acute infectious enteritis with a polyneuritic syndrome. Amer. Jour. Med. Sci., 1920, clx, 52.

Hvoker, R. G. The treatment of staphylococcus septicemia by transfusion of immune blood. Ann. Surg., 1917, lxvi, 513.

Lartigau, A. J. The bacillus pyocyaneus as a pathogenic factor in human pathology, with the report of 3 cases. Phila. Med. Jour. 1898, ii, 562.

Rueok, G. A. Staphylococcus septicemia complicated by subpectoral abscess. Med. Rec., 1915, lxxxviii, 105.

Sherwood, W. A. Report of a case of true staphylococcus pyemia treated exclusively with vaccines. N. Y. State Med., 1911, xi, 172.

Soper, W. B. A series of cases of staphylococcus aureus sepsis. N. Y. Path. Soc. Proc., 1911–12, xi–xii, 223.

Taylor, K. Treatment of bacillus procyaneus infection. Jour. Amer. Med. Assoc., 1916, lxvii, 1598.

Colon Bacillus Septicemia

Blackader, A. D., and Gillies, B. D. General infection by the colon bacillus with rapidly fatal septicemia and hemoglobinemia. N. Y. Med. Jour., 1907, lxxxv, 483.

Enright, J. I., and Barr, P. H. On a pyemia due to organisms of the bacillus coli group occurring in Turkish soldiers. Lancet, 1918, cxcv, 585.

Holzman, A. Two cases of colon bacteremia. Long Island Med. Jour., 1913, vii, 376.

Moorhead, T. G. The bacillus coli communis is a cause of septicemia. Practitioner, 1905, lxxiv, 770.

Rochester, D. A case of colon bacillus septicemia. Jour. Amer. Med. Assoc., 1907, xlviii, 774.

Bacillus Pyocyaneus Septicemia

Barker, L. F. The clinical symptoms, bacteriologic findings and postmortem appearances in cases of infection of human beings with the bacillus pyocyaneus. Jour. Amer. Med. Assoc., 1897, xxix, 213.

Bollag, K. Zur Bekämpfung der Infection durch den Bacillus pyocyaneus. München. med. Wochen., 1914, lxi, 2356.

Brill, N. E., and Libman, E. Pyocyaneus bacilliemia. Amer. Jour. Med. Sci., 1899, cxvii, 153.

Camp, de la. Zur kennturis der Pyocyaneussepsis. Charite-Annalen, 1904, xxviii, 92.

Clarke, J. M. A case of acute septicemia due to the bacillus pyocyaneus. Bristol Med. Chr. Jour., 1913, xxxi, 4.

Eastman, J. R., and Keen, T. V. Bacillus pyocyaneus septicemia associated wtih blastomycetic growth in primary wound. Ann. Surg., 1904, xl, 613.

Freemann, L. Chronic general infection with the bacillus pyocyaneus. Trans. Am. Surg. Assoc., 1916, xxxiv, 113; also Ann. Surg., 1916, lxiv, 195.

Hess, A. F. A case of sepsis due to bacillus pyocyaneus. Proc. N. Y. Path. Soc., 1910, ix, 158.

Horder, T. J. A case of pyocyaneus pyemia following otitis media. Trans. Path. Soc., 1904, lv, 140.

Lartigan, A. J. The bacillus pyocyaneus as a pathogenic factor in human pathology, with the report of three cases. Phila. Med. Jour., 1898, ii, 562.

Perkins, R. G. Report of 9 cases of infection with bacillus pyocyaneus. Jour. Med. Res., 1901, vi, 281.

Roberts, J. B. A fatal case of bacillus pyocyaneus septicemia after surgical operation. N. Y. Med. Jour., and Phila. Med. Jour., 1905, lxxxii, 313.

Taylor, K. Treatment of bacillus pyocyaneus infection. Jour. Amer. Med. Assoc., 1916, lxvii, 1598.

Wait. Contribution to study of pyocyaneus infections. Jour. Infec. Dis., 1908, v, 542.

Bacillus Mucosus Capsulatus

Whiting, F. The insidious latent period of streptococcus mucosus. Trans. Amer. Otol. Soc., 1912, xii, 575.

Micrococcus Tetragenous

Anglada, J. Septicemie a tetragenes a fonne de fievre continue, avec phlegmous, bubons et abies multiples. Himoculture positive. Montpelier, Med., 1911, xxxiii, 392.

Birks, A. H., Thornley, R. T., and Fawcus, R. A. Septicemia due to micrococcus tetragenous as a cause of pyrexia at the front. Quart. Jour. Med., 1916–17, x, 1.

Byers, Sir J., and Houston, T. Tetragenous septicemia. Lancet, 1913, i, 1723.

Rogers, H., and Tremolieres. Septicemie a tetragene. Bull. et Mem. Soc. med. des Hop. de Paris, 1906, 69.

Oettinger et Malliovel. Septicemia a tetragene. Bull. et mem. Soc. med des Hop. de Paris, 1906, p. 123.

Josue et Lian. Septicimie a tetragene. Bull. et Mem. Soc. med. des Hop. de Paris, 1906, 188.

Robinson, H. A case of tetragenous septicemia. Lancet, 1915, i, 1287.

Pneumococcus

Rueck, G. A. A case of pneumococcus septicemia. Med. Rec., 1913, lxxxiv, 1033.

Meningococcus

Andrews, F. W. A case of acute meningococcal septicemia. Lancet, 1906, i, 1172.

Bovaird, D. Jr. Meningococcus septicemia with sterile cerebrospinal fluid. Presbyterian Hospital, N. Y. City, 1908, viii, 355.

CHAPTER LIV

GLANDULAR FEVER

BY WALTER F. WATTON, M.D.

Definition, p. 457; Etiology, p. 457; Symptomatology, p. 458; Diagnosis, p. 459; Complications, p. 459; Treatment, p. 459; Prognosis, p. 460; Pathology, p. 460; Bibliography, p. 460.

Definition.—Glandular fever is an acute lymphadenitis of children of undetermined etiology, characterized by an inflammatory swelling of single groups of glands, such as the anterior cervicals. It is accompanied by fever, constipation and a considerable degree of anemia and depression.

Etiology.—The exciting cause of glandular fever is not known. Since the original work done by Pfeiffer in 1889 there have been many conflicting reports as to the etiology. Recently on several occasions the streptococcus has been cultured from the involved gland. Other competent workers have isolated the pneumococci, the diphtheroid bacilli and the staphylococci. Still other individuals hold the theory that it is an auto-intoxication possibly of intestinal origin. The almost constant presence of intestinal stasis or occasionally severe diarrhea led Stark to advance the theory that the general symptoms and also the adenitis might be due to absorption of toxins aided by intestinal disorder.

Most of the cases of glandular fever which have been reported have occurred during the colder months from October to March. In the largest epidemic reported, which occurred in 1896, nearly all of the cases occurred in October. Males are affected a little more frequently than females. Newman reported that in his cases 70 per cent. were boys. Other observers have not noted any predominence in males.

The disease is practically limited to childhood, very rarely have cases been reported after puberty. In fact, under 18 months children are often attacked but it rarely occurs under six months.

Dankin has described a few instances in which young adults were afflicted. In the epidemic described by West the cases ranged from seven months to thirteen years. Five-sixths of the total number were under five years of age.

The disease has been described in other than the white race with no variation of symptoms. Hereditary or family predisposition seems to play no part. Direct exposure seems to be the important factor in transmission. Most all children who lived in the household where the condition existed contracted the disease. It is not readily conveyed by a third party. The children who contracted the disease were not necessarily under-nourished. The general physical condition of the individual seemed to play little part in the susceptibility of the individual.

Some are of the belief that previous tonsillectomy offers some protection but this is not at all a constant observation in the cases reported. The epidemics that have occurred have been mainly in the country districts or small towns where the removal of tonsils is not as commonly practiced as in the cities.

Glandular fever is not an institutional disease. Poor ventilation and very intimate contact was reported to exist in most of the families where the greater number of children were attacked.

The disease occurred in narrowly limited epidemics.

The incubation period is 5 to 10 days; average is 7 days.

Symptomatology.—The onset of the disease is rather sudden, often with no prodromata. The child complains of not feeling well, awakens several times in the night, and complains of headache. Pain in the abdomen accompanied by nausea and vomiting develops. The child refuses food and is noted to hold the neck stiffly. There is a picture of a general or possibly a local infection, as manifested by the general malaise and the constitutional symptoms. The headache, nausea, vomiting, and pain in the legs are quite disturbing symptoms and persist.

The most characteristic feature of the disease is the swelling of the cervical lymph glands which began to be involved a few hours after the premonitory symptoms. The anterior cervical glands on the left side are as a rule the first to become enlarged. At first a single gland is noted about the size of an almond. These increase and more become involved making a mass extending down the neck just in front or beneath the sternocleidomastoid muscles. The glands nearest the ear are usually the most prominent. These glands are tender and are painful on movements of the neck. The posterior cervical glands are shotty and palpate as strings of small beads. If the swelling remains unilateral the condition usually subsides on the second to the fourth day. In nearly 50 per cent. of the cases the glands of the opposite side of the neck become involved but never simultaneously with those of the left side. Some of the other lymph glands of the body, such as the axillary, mesenteric and inguinal, are often enlarged. As each group of glands are attacked there is a corresponding elevation of temperature. The mesenteric glands are the most frequent accompanying glandular involvement. The spleen is practically always moderately enlarged. The liver is sometimes palpated. The temperature during the first two days ranges from 101° to 103° F. (38.3° to 39.4° C.). It then may fall by crisis or may remain high as long as groups of glands are enlarged. It is intermittent in type and seems to depend upon the degree of glandular involvement. As new lymphoid tissue is invaded the fever increases.

One of the striking features of glandular fever is the fact that the throat is normal. Very rarely is there ever any distinct redness of the pharynx noted. A slight cough may be present but it is not the rule. The cough is unproductive. At times it is spasmodic and in some cases resembles croup.

Auscultation of the chest reveals nothing abnormal. Signs indicating enlargement of the bronchial glands have never been found in any cases reported. However, but very few observers have noted the presence or absence of a D'Espign sign.

The heart rate is increased but there is not a corresponding increase to the elevation of temperature. The rate is from 100 to 120. It seldom reaches over 140 even in young children with a high temperature.

A systolic murmur is not infrequently heard at the apex of the heart. Continued observation proves this murmur to practically always be functional in character. The blood examination shows a moderate leukocytosis—from twelve to eighteen thousand. The hemoglobin and red cells show a slight secondary anemia. The differential counts have varied considerably as reported by different observers. Many have reported a moderate increase in the lymphocytes, but considering that these counts were made on children the increase is not sufficient to be ordinarily considered abnormal.

The urine occasionally shows a hematuria and quite often also other signs of an acute nephritis. A small amount of albumin and small granular casts are found in these cases.

Diagnosis.—The diagnosis of glandular fever is made by its epidemic character, its sudden onset accompanied by enlargement of the cervical glands where there is no local focus of infection that could account for the glandular enlargement. From mumps the disease can be rather easily differentiated for the parotid gland is never involved. When the mesenteric glands are enlarged the differential diagnosis is more difficult and often only a tentative diagnosis can be made until the outcome of the case is known.

Complications.—Complications are rare, the most frequent being nephritis which may be accompanied by hematuria. The heart murmurs prove to be functional and the heart muscles are not especially affected.

Suppuration of the glands never occurs in a case of true glandular fever.

Treatment.—The treatment is mainly symptomatic. To the swollen glands local applications are of little or no value. **Mild counter-irritants,** as camphorated oil or tincture of iodin, may be used. It is well to keep a flannel cloth about the neck for the purpose of maintaining an even temperature over the surface of the swelling. This at least adds to the comfort of the patient.

Fluids should be forced, especially water. It is very desirable to have the child take a total of **2** or **3 quarts of liquids a day,** including the liquid diet. About **40 grains of sodium bicarbonate** per day should be given to help preserve the alkaline balance of the blood.

Acetyl salicylic acid or **salyprin** in **1** or **2 grain** doses may be administered in powders with **lactose** or in a **thick syrup** in the form of an emulsion. This form of salicylate aids greatly in relieving the pain and thus permitting the child to obtain rest. Frequent **tepid sponges** followed by **alcohol rubs** are very desirable to combat the hyperpyrexia and stimulate the circulation.

The bowels should be kept active by **mild cathartics.**

Convalescence is sometimes prolonged, the child being left depressed and anemic. The great majority of cases run a short course of three to ten days. In cases where many lymph glands are involved the condition persists for a month or more and lowers the child's resistance to such a degree that some intercurrent infection may prove fatal.

Prognosis.—In general the prognosis is favorable. In but one case of those described by West did the child die and this individual was delicate and convalescing from scarlet fever.

Pathology.—Little is known of the pathology of glandular fever as practically all the cases recover and careful microscopic studies have not been available.

BIBLIOGRAPHY

JAMISON, S. C. Glandular fever. New Orleans Medical and Surgical Journal, Jan. 1923.

KOPLIK, H. Glandular fever. Diseases of Infancy and Childhood, 1906, 308.

PFEIFFER, E. Drusenfiber. Jahrbuch für Kinderheilkunde, 1889, xxix, 257. Abstracted in Arch. of Pediat., vii, 326.

POMBRAK, A. E. Case of glandular fever complicated with hemorrhagic nephritis. Med. Obozr. Msk., xliii, 1126.

ROSENBLÜTH, M. B. Glandular fever. Med. Clin. of North America, July, 1920, iv, No. 1.

RUDOLPH, R. D. Epidemic cervical adenitis. Brit. Med. Jour., 1897, i, 160.

STARK, A. C. Glandular fever. Brit. Med. Jour., 1914, i, 195.

WEST, J. P. An epidemic of glandular fever. Arch. of Pediatrics, 1898, 13, 889.

WILLIAMS, D. Glandular fever. Allbutt's System of Medicine, 1898, 716.

CHAPTER LV

APHTHOUS FEVER

By Walter F. Watton, M.D.

Definition, p. 461; Etiology, p. 461; Symptomatology, p. 461; Diagnosis, p. 462; Treatment, p. 462; Prognosis, p. 462.

Aphthous fever is an acute contagious disease characterized principally by the appearance of small vesicles in and around the oral and pharyngeal mucous membranes and the labial and nasal muco-cutaneous junctions. It is a disease of rather infrequent occurrence in man. No age or sex has any particular susceptibility, except that inasmuch as the source of contagion is from the foot and mouth disease in cattle, adult males, being those more numerously engaged in the handling of cattle and their hides, are more exposed to contagion.

Etiology.—The particular bacteria responsible for the lesions have not been isolated, but it has long been demonstrated that the disease in man is identical with the foot and mouth disease in cattle, sheep and pigs. The epidemiology, insofar as there has been in any locality such numbers of cases as might permit the use of the term epidemic, is parallel with the analogous disease in cattle. However, it must be borne in mind that there have been widespread and rapidly moving epidemics of foot and mouth disease which have not been paralleled by any corresponding outbreak of aphthous fever in man. Cattle which have been affected may act as carriers many months after recovery.

The transmission to man is from the secretions of the animal directly to the mucous membranes or cutaneous surface by means of the hands or implements of the household or dairy barn, cattle yard and slaughtering places; or on the other hand, through the milk of the cow. It has not been demonstrated that it is possible to contract aphthous fever by eating the flesh of an animal at any time affected with the foot and mouth disease.

Symptomatology.—In the beginning there are the usual signs of inflammation: redness of the mucous membrane, dryness of the mouth, a slight increase in temperature with increased thirst, followed in a few hours by the appearance of small discrete vesicles on the edges of the tongue, on the lips and occasionally on the cheeks and about the nares. It is not at all rare to find these lesions on the tips of the fingers and at the base of the nails. These vesicles soon become confluent and form large blebs. In rare instances these blebs appear over the surface of the body. The vesicles are not umbilicated and at their appearance the temperature falls to normal where it remains throughout the course of the disease unless secondary infection supervenes. With the appearance of the vesicles on the buccal surface there is increased secretion of saliva, which sometimes becomes excessive in children who have been infected by direct contact or through milk. The disease lasts for a few days and gradually subsides, the vesicles and blebs drying and leaving scabs which readily drop off with no appreciable scar remaining.

Diagnosis.—During the prevalence of foot and mouth disease among domestic animals the appearance of aphthae should be regarded as at least suspicious of aphthous fever and should be definitely diagnosed from aphthous stomatitis and ulcerative stomatitis. In aphthous stomatitis the history of contact is usually wanting and secondary inoculation from the patient to another person is not possible.

The lesions in ulcerative stomatitis show destruction of tissue at the base of the vesicle, the history of contact with infected animals may be absent and reinoculation does not obtain.

Treatment.—Prophylactic measures should be established at the outbreak of foot and mouth disease in animals. All attendants upon such animals should take every precaution as to cleanliness and avoidance of contact of any cuts or erosions of the skin with the secretions of such animals, both salivary and mammary. Milk, meat and hides from infected animals should be destroyed.

The active treatment consists of such local measures as will control the pain, reduce the inflammation, and prevent infection of other persons. The use of **liquor antisepticus alkalinus** as a **mouth wash** in full strength for adults and in half strength for children is advocated. The ulcers may be touched with **nitrate** of **silver** and **chlorate** of **potash** used as a gargle.

Prognosis.—The disease is rarely fatal, except in marantic infants.

CHAPTER LVI

WHOOPING COUGH

(PERTUSSIS)

By Mansfield G. Levy, M.D.

Definition, p. 463.
Etiology, p. 463; Exciting causes, p. 464; Infective period, p. 464; Incubation, p. 464.
Symptomatology, p. 464; Catarrhal stage, p. 464; Spasmodic stage, p. 464; Stage of decline, p. 465; General features, p. 465.
Diagnosis, p. 465.
Complications, p. 466.
Treatment, p. 466; Prophylaxis, p. 466; General management, p. 467.
Prognosis, p. 468.
Pathology, p. 468.

Definition.—Pertussis is a specific, acute, contagious and infectious disease caused by the Bordet-Gengou bacillus and transmitted almost entirely by direct contact. It is characterized by signs and symptoms that arise as the result of the inflammation along the respiratory tract. The most notable of these are the spasmodic attacks of coughing, which in the later stages of the disease are characterized by the significant and well-recognized inspiratory whoop.

Etiology.—PREDISPOSING CAUSES.—Pertussis may occur at almost any time of the year, but is especially liable to occur during the cold seasons when the respiratory tract seems especially sensitive. However, epidemics during the summer have been known to occur. Luttinger reports a series of 6,868 cases which showed a decided prevalence during the summer.

An analysis of 2,000 cases which were reported to the New York Health Department Clinic several years ago proved 80 to 85 per cent. of the cases to be in children between two and five years of age. Young infants are very susceptible.

There is a definite sex incidence in this disease, approximately 55 per cent. of the cases occur in girls and 45 per cent. in boys.

The disease is common to all races. The negro population in America are somewhat more susceptible than the white. It is quite common among the American Indians, the Filipinos and the Japanese.

While it would seem natural that a debiliated child, one that is marantic or wasted from some chronic infection, should more easily become infected, yet such is not the case. Simple exposure is usually sufficient to cause contamination regardless of the physical condition of the child. While the estimate may seem high, the author feels that about 90 per cent. of the children exposed to the infection show actual involvement with the disease. A previous attack almost always insures against subsequent attacks.

Exciting Causes.—Pertussis is undoubtedly the result of the specific organism, the Bordet-Gengou bacillus. While it is true that various organisms have been found in the sputum and the excretions of the respiratory tract yet it is equally true that the Bordet-Gengou bacillus will commonly be found when looked for early in the disease and when properly cultured. Bordet and Gengou in 1906 published a work in which they claimed to have separated a definite organism as the cause of pertussis and that they had been able to culture it. Their report is here quoted in part: "The bacillus is a small ovoid bacterium which cannot be cultivated on agar, gelatin or common bouillon, but can be cultivated only upon blood agar. The first generations grown on blood agar grow sparsely but later generations grow abundantly. The small round colonies which develop in two to four days are gray in color, shimmering like quicksilver. The bacillus is hemolytic. It is much like the influenza bacillus but differs therefrom in that it is agglutinated by whooping cough immunization serum, which is produced through the injection of whooping cough emulsions in rabbits."

Klimenko has been able to confirm the above-quoted findings, as has also Rafael Kirkland in his treatise on whooping cough written in 1917.

Infective Period.—Whooping cough may be communicated from the very beginning of the catarrhal stage, in fact this is the most contagious period. It seems to be contagious throughout the period of spasmodic coughing, yet after two or three weeks much of the infectivity is lost. The source of the contagion is the patient, almost never the room or the clothing.

Incubation.—This is rather indefinite, but is thought to be from seven to fourteen days. It would seem perfectly safe to say that the disease had not been contracted if after sixteen to eighteen days beyond exposure no cough develops.

Symptomatology.—It has been customary to divide the course of this disease into three stages, catarrhal, spasmodic and stage of decline.

Catarrhal Stage.—In the catarrhal stage, which lasts from three to fifteen days, there is sneezing, coughing, possibly a slight temperature, the usual signs of a naso-pharyngitis. The cough in this stage is usually more or less spasmodic, but does not have the characteristic whoop; nor does it moderate with treatment. This is the time of greatest infectivity.

Spasmodic Stage.—During the spasmodic stage, the cough becomes quite characteristic. The patient is seized with a series of severe coughing attacks, each one represented by a succession of short coughs with progressive severity terminating in an inspiratory whoop, followed by the expulsion of mucus from the respiratory tract or a simultaneous vomiting of mucus and food content of the stomach. The eyes are suffused and frequently there is hemorrhage into the conjunctiva or from the nasal mucous membranes. These paroxysms commonly occur spontaneously but may be brought on by the swallowing of food or by overactivity. The paroxysms may be momentary in duration and then again may last for from two to five minutes. Some children are more or less exhausted by the attacks, while others are not so severely affected. Some cases show many daily paroxysms numbering twenty-five to fifty and others show few, ten to twenty. Quite commonly, especially in younger children, vomiting follows the paroxysms. Convulsions may occur during this stage, but when they do occur, they are usually secondary to some complication such as bronchopneumonia.

STAGE OF DECLINE.—During the stage of decline, the paroxysms decrease not only in number but also in severity. The decline covers a period of from two to four weeks.

VARIATIONS IN THE COURSE.—Occasionally one sees cases of pertussis completed in from two to four weeks. It is not now uncommon to see them completed in less time even than this, owing to the newer and more successful methods of treatment. But there are abortive types of cases where but few attacks occur. Even these are not typical, being free from spasm or whoop. Then, there occur cases in which there is an annoying, persistent and irritative cough extending over a period of several weeks without the development of spasm or whoop. Here diagnosis is difficult. However, a history of exposure and a blood examination will usually suffice to make a diagnosis positive. This is the type of case that occurs in late childhood or in adult life. On the other hand, especially severe cases are not very common. The more severe cases seem to occur in children who either are or have been spasmophilic. Occasionally we see epidemics where the infection seems especially virulent. These cases show a distinct rise in temperature—aften to 102° F. (38.2° C.)—and the general well-being of the child is markedly impaired by restlessness and loss of sleep. Dyspnœa and frequent exhausting attacks of coughing and vomiting occur. These cases, occurring as they do without complications, may lead speedily toward death.

Whooping cough in very young infants often presents some peculiar characteristics. The spasmodic coughing attacks occur so acutely and with such severity as to cause cyanosis and apnœa with resulting unconsciousness, eclamptic convulsions, and general wasting. The raising of mucus and the occurrence of vomiting do not appear in these cases. Hence, diagnosis is difficult and here again depends upon the blood finding, the sputum examination and the history of exposure.

GENERAL FEATURES.—Because of the always present bronchitis, the physical examination of the chest will reveal signs of the bronchitis. Some fine crackling râles can always be heard over the smaller bronchi and bronchioles while the peri-bronchial glandular involvement is determined by x-ray examinations and the positive D'Espine. This peribronchial glandular involvement disappears as the disease clears up.

Diagnosis.—One of the diagnostic features of the disease is the constant early leukocytosis of 15,000 to 25,000 with a preponderance of 60 to 75 per cent. lymphocytes. This sign can be recognized some time before the characteristic whoop develops. A well-marked iodophilia is also present. The presence of an ulcer about the frenum of the tongue occurs quite commonly, especially in younger children. The urine in cases of pertussis shows nothing abnormal as a rule, although glycosuria has been reported by Crisalfi, and transient albuminurias, with hyalin casts, have been reported by Knight.

A positive diagnosis can be made only by isolating the infecting organism, the Bordet-Gengou bacillus, or by hearing a typical paroxysm. Without these, a presumptive diagnosis, which will usually be correct, can be made. A persistent cough without whoop that will not yield to ordinary treatment and having a tendency to occur mostly at night and which is spasmodic in type, also is presumptive evidence of pertussis. The blood-picture is a distinctive feature which leans towards diagnosis early in the disease. The presence of an epidemic should also be considered when one weighs the question of pertussis. The agglutination test and the method of compliment deviation are not practical for diagnostic purposes because they are available only late in the disease and can be accomplished only in properly equipped laboratories.

The early diagnosis of whooping cough presents real and practical difficulties to the practitioner. A child with an apparently harmless, simple cough is permitted to mingle with and infect other children because a diagnosis of the infectious character of the disease has not been recognized. Jacob after serious investigation believes that every case of suspicious cough in which there was marked conjunctival congestion in the region of the external canthus subsequently developed whooping cough and that this local congestion appears very early in the disease, much earlier than the characteristic whoop. In examining for this sign the patient is directed to look toward the nasal side of the eye being examined, when on separating the lids at the external canthus a tumid congested area somewhat resembling a phlyctenule will appear on the bulbar conjunction just within the external canthus.

Complications.—The most common of the complications of pertussis are those connected with the respiratory system. Tubercular infection, previously inactive because of the child's natural resistance, may become active. Hemorrhages into the mucous and serous membranes, commonly the meninges and also within the skin may occur; the most common form of hemorrhage is nasal. Bronchopneumonia is probably the most frequent cause of death in pertussis. It is especially apt to develop in infants and very young children when measles occur coincidently. The bronchopneumonia always makes its presence known by an abrupt rise in temperature. Physical examination of the chest may reveal but little because the areas of involvement may be small. During the course of the bronchopneumonia, the whoop is apt to disappear, only to return again as the bronchopneumonia clears up. Bronchitis, of course, is commonly associated with and is actually a part of the disease. When measles, scarlet fever, or diphtheria complicate pertussis, the outlook is gloomy. Meningitis, middle ear infection, and gastroenteritis occasionally follow whooping cough. True nephritis has never been seen to complicate pertussis, in the experience of the writer, although cases are reported in the literature.

Treatment.—PROPHYLAXIS.—Absolute isolation both within and without the family is essential in preventing the spread of the disease, since it spreads only by direct contact. It is wise to be especially scrupulous as regards isolation in the schools, nurseries and in all places where children congregate. Sputums and vomited material should be burned. Vaccines, serums and bacterins have been useless as prophylactics according to many workers; on the other hand, some successes have been reported.

General Management.—Fresh air is important. One who has had any experience in cases of pertussis knows that the spasms of coughing are much less frequent while the patient is out of doors than while indoors. This form of treatment must be carefully prescribed in emaciated children and must be interdicted altogether in children with a complicating and especially active bronchitis. Oftentimes a change of climate and of environment has a beneficial effect.

A simple diet, easy of digestion, is the diet of choice. Meals should be light and especially frequent, since vomiting so commonly occurs. As to the use of drugs, myriads of these have been tried. This only proves the inadequacy of them. The various antispasmodics, chief of which is benzyl-benzoate, have not been of any avail in the writer's hands, even when especially large doses were used. On the other hand, it has been his experience in a number of cases to have caused gastric upsets with this particular drug. The spraying of the nose and throat and the application to the larynx of adrenalin has been of no avail. While the writer has not used the intramuscular injection of ether he has no doubt this method of treatment possibly might be of some avail, since it has been found so by many competent clinicians. Cocaine has been of some help, but is a dangerous drug. Potassium chlorate, quinin, antipyrin, salicylic acid, belladonna, the bromides, opium, chloral and pertussin are only a few of the various drugs that have been used to alleviate the spasms of pertussis with more or less success.

While vaccines, sera and bacterins have been reported by various investigators to be of little or no avail, the hope of the future, so far as pertussis is concerned, seems to lie in this direction.

The author, as the result of a rather large experience with vaccines and bacterins, is of the opinion that much success in treatment may be had in a large number of cases of pertussis by their administration and has almost entirely eliminated pharmaceutical preparation in pertussis therapy.

Vaccines and bacterins must be freshly prepared and given in heavy dosage. Care must be exercised in their administration to young children as the fright occasioned by the subcutaneous injection often produces more frequent paroxysms of coughing. Real tact upon the part of the physician is of great value in dealing with the young whooping cough patient.

When convulsions occur during the course of the disease, it is necessary that this serious condition be met as any eclamptic condition be met. The quickest and most lasting relief can be had from lumbar puncture. Any other complications or conditions are met and treated as they arise and as the course of the disease indicates.

The following table will indicate the frequency and dosage in units in the administration of pertussis vaccine:

TABLE I.

Age	1st Day	3d Day	5th Day	7th Day	9th Day
Under 1 year......	250 million	500 million	1000 million	2000 million	4000 million
Over 1 year.......	500 million	1000 million	2000 million	4000 million	8000 million
Adult	1000 million	2000 million	4000 million	8000 million	

Yankhauer advocates the direct application of a solution of antipyrin to the larynx and vocal cords. Reasoning that whooping cough is a local inflammation of the respiratory tract caused by a focal infection and that antipyrin is an antiseptic, an astringent and mild local anæsthetic he exposed "the larynx with a direct laryngoscope, using for this purpose the Jackson instrument, and with a syringe armed with a straight cannula of the proper length, injecting 20 to 30 minims of a 4 per cent. solution of antipyrin directly upon the vocal cords. The injections are made once a day." He has had great success with this method especially in reducing the severity and frequency of the paroxysms.

Recently some investigators have experimented with x-rays in the treatment of pertussis. The reports, as yet, have not been sufficiently numerous to determine its value.

Prognosis.—The mortality rate in pertussis is rather higher than it should be. This is explained by the fact that the disease occurs in children and is especially apt to occur in very young children who are prone to respiratory complications. Bronchopneumonia, convulsions or brain hemorrhage may occur and of course the outlook under these circumstances is not so favorable. The occurrence of cerebral hemorrhage during pertussis is commonly of the hemiplegic type and is not often fatal; in fact the paralysis which occurs as the result of this hemorrhage is not even lasting in most of these cases. The younger the child, the greater the mortality rate; in fact, the great majority of deaths in whooping cough occur between six months and two years of age. Another source of great danger in whooping cough is the occurrence of convulsions. Because this is a serious occurrence, the writer does not feel justified in using ordinary means to control it and usually resorts immediately to lumbar puncture.

Pathology.—Because death rarely occurs from pertussis per se, being due commonly to some complication, the opportunity for pathological studies has been meager. The changes that occur no doubt are very trivial and consist merely of catarrhal inflammations of the respiratory tract.

The blood, of course, shows a decided pathological change with a hyperleukocytosis, of which increase the lymphocytes are in much the greater proportion. The heart rarely shows evidence of added burden in the way of hypertrophy. Where the burden is great, right-sided dilatation rather than hypertrophy may be found. In the gastro-enteric tract, we find again not uncommonly evidence of a catarrhal inflammation. Rarely do we find petechial hemorrhage of the meninges nor do we find any ot the signs of congestion or inflammation of these appendages.

BIBLIOGRAPHY

Auricchio, L. La terapia dolla pertossi. La Pediatria, 1920, xxix, 1009.

Bordet and Gengou. Coqueluche, 1906.

Klimenko. Centralbl. f. Bacteriol., Jena, Abt. 1, Originale, 1908, 1909, xlviii, 64.

Kirkland, R A treatise on pertussis. Kirkland, 1917.

Luttinger. American Jour. Dis. of Children, 1906, xii, 290.

Meyer, A. H., and Chievitz. The bacteriology of whooping cough. The Lancet, 1916, par. 1063.

Nobecourt. Infections desvoies respiratpries. Bronchits and bronchopneumonies demsla coqueluche. Prog. Med., 1922, xxix, 1009.

Sedgwick and Scherer. Feers Pediatrics, p. 672.

Talbot, F. Whooping cough. Med. Clin. of N. Amer., 1920, p. 1177.

Yankhauer, Sidney. The laryngoscope, February, 1921.

CHAPTER LVII

TAPEWORMS AND FLUKES

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Cestodes, p. 471—*Tænia saginata*, p. 473—*Tænia solium*, p. 473—*Tænia confusa*, p. 474—*Tænia echinococcus*, p. 474—*Echinococcus multilocularis*, p. 476—*Hymenolepis nana*, p. 476—*Hymenolepis diminuta*, p. 477—*Dibothriocephalus latus*, p. 477—*Diplogonoporus grandis*, p. 477—*Dipylidium canium*, p. 478—*Davaninea madagascariensis*, p. 478—*Sparganum mansoni*, p. 478—*Sparganum proliferum*, p. 478.

Trematodes, p. 479—Hepatic distomiasis, p. 479a—*Clonorchis sinensis*, p. 479a—*Fasciola hepatica*, p. 479b—*Opisthorcis filineus*, p. 479b—*Dicrocœlium lanceatum*, p. 479b—Pulmonary distomiasis, p. 479c—Venal distomiasis, p. 479c—*Schistosoma hematobium*, p. 479c—*Schistosoma mansoni*, p. 479d—*Schistosoma japonicum*, p. 479d—Intestinal distomiasis, p. 480.

Cestodes (tapeworms) and trematodes (flukes) form the two great classes of plathelminthes, or flat worms, which are of importance in human parasitology.

CESTODES

The cestode is an obligate endoparasite of certain lower animals and of man. The adult stage, found in the intestinal lumen, is the worm, made up of a scolex or head, bearing a suction apparatus, armed or unarmed, for the purpose of attachment to the mucous membrane of the duodenum or jejunum; non-segmented neck; and a segmented trunk or strobila. There are nervous and excretory systems, but the digestive tract is wanting. Nutrition is accomplished by osmosis. The segments, or proglottides, are produced in a continuous series by budding from the neck and come to lie in the long ribbon-like arrangement which suggests the name of tapeworm. As the chain extends, the segments caudad mature, each with a complete bi-sexual genital system. The cestodes are therefore hermaphroditic. The strobila varies in length from a few millimeters (*Hymenolepis nana*) to about 10 meters (*Tænia saginata, Dibothriocephalus latus, Diplogonoporus grandis*); the number of segments ranges between 3 to 4 (*Tænia echinococcus*) and 4000 (*Dibothriocephalus latus*). Aged segments break off singly or in short chains and are lost in the feces.

The eggs possess a soft shell which, however, has not infrequently been digested away before discharge per anum from the host; within the shell is the embryophore containing the six-hooked embryo or oncosphere. Eggs do not usually hatch until ingested with food or water, when the larva escapes, bores through the mucous membrane of stomach or intestine, and comes to rest in muscle, liver, lung, brain or other organ in the cysticercus stage. When the containing tissue is in turn ingested and digested away, the immature scolex of the cysticercus is freed, attaches itself to the wall of the intestine, and develops the mature worm. Usually two hosts are required for the entire life history of the parasite; but it should be noted that both sexual and asexual cycles may occur, wholly or in part, in the same human host in the cases of *Hymenolepis nana* and *Tænia solium;* and that in one instance (*Tænia echinococcus*) it is the lower animal which harbors the adult worm and man who suffers from the cysticercus stage (echinococcosis). Tæniasis may therefore be intestinal or somatic.

SYMPTOMATOLOGY.—The symptoms of intestinal tæniasis are, on the whole, vague. There may be indigestion, colic, anorexia or, more rarely, bulimia, giddiness, headache, tinnitus, syncope, disorders of vision, sometimes with anisocoria, salivation, nasal and anal pruritus, pain or a sense of weight or movement in the abdomen, pains and lassitude in the limbs, anemia, emaciation. The anemia may follow infestation with *Dibothriocephalus latus, Tænia saginata,* and *Tænia solium* (in the order of severity).

The symptoms of somatic tæniasis vary with the location and number of the cysts and are largely due to pressure.

DIAGNOSIS.—Diagnosis of intestinal tæniasis is made by identification of the eggs or of the segments in the feces. *Cysticercus cellulosæ* (*Tænia solium*) of the brain is difficult to diagnose, but when it occurs just under the skin the excised specimen may be identified with the microscope. Diagnosis of echinococcosis will be considered under *Tænia echinococcus.* In searching for segments a small bit of feces on the end of a match is rubbed up in a drop of water on a glass slide and inspected with the low dry lens. The high dry lens is powerful enough for further identification. Characteristics of the gravid uterus are visible when the segment is pressed between glass slides and held to the light. Staining methods for the uterus are described (*vide* bibliography).

PROPHYLAXIS.—Prophylaxis is mainly a matter of thorough cooking of meat and fish. Hands should be washed and nails should be cleaned before meals especially after fondling animals. Human feces should be so disposed of as to avoid infection of the lower animals, especially the coprophagous pig (*Tænia solium*). Inspection of meat at the abattoir should be strict and constant. Cold storage for three weeks may destroy the larvæ of *Tænia saginata* in beef, but is not sure for *Tænia solium* in hogs. The danger of autoinfection with the cysticercus of *Tænia solium* makes prompt treatment imperative once the worm is discovered.

TREATMENT.—Treatment of intestinal tæniasis is carried out with any of the standard tæniafuges. For twenty-four hours before the dose is given the patient fasts or is allowed only a very light diet, since it is important that the action of the drug upon the worm be not hampered by the presence of intestinal contents. One or two small doses of a purge may be given and the colon should be cleansed with an enema the night before and possibly again on the morning of the treatment, in order to afford the stupefied worm free exit.

The tæniafuge in commonest use is **male fern** (oleoresin of aspidium). The ethereal extract should be fresh and potent. The dose as given by Stiles is **2** to **8 grams** (**½** to **2 drams**). It may be given in simple syrup, but probably it is better to put it in hard gelatine capsules, which may be made "enteric" by a coating of salol or keratin or by treatment with formaldehyde. One quarter of the amount is given by mouth every fifteen minutes, early in the morning and on a fasting stomach; the patient would better remain in bed through most of the day. From thirty to sixty minutes after the completion of this dosage a full saline purge is given. Oil is avoided, since it tends to promote absorption of the drug. Toxic symptoms include headache, dizziness, dyspnea, delirium, stupor; fatal cases have been reported, usually after much larger doses. Following the purge the patient should be instructed to defecate into a warm vessel containing water at body temperature, since contact of the warm with a cold surface may stimulate contraction of the worm's musculature with breakage of the strobila and partial retention of the parasite. Passage of the worm is often slow and both host and physician must be patient if the all-important scolex is to be secured. When passage seems to be complete the worm is carefully washed from the feces, and most carefully inspected, preferably on a dark-colored plate or platter. Great care must be taken to identfy the head, since if this remains in the host a new strobila will form and the treatment be a failure. Sometimes, however, the scolex is passed but not recognized; this may be assumed if after several months and repeated examinations no segments or eggs are found in the stools.

Other tænifuges used are cusso, kamala, bark of fresh pomegranate root, pepo (perhaps best for children), santonin, thymol, etc.

Tænia Saginata

(fat tapeworm, beef-measly tapeworm, unarmed tapeworm)

MORPHOLOGY.—4 to 10 meters by 4 to 12 millimeters. Scolex with four cup-like suckers, not provided with a circlet of hooks (rostellum). Segments number up to 1000; gravid segments 12 to 20 mm. by 4 to 6.5 mm.; escape singly or in pairs; may be found in clothing or bed; possess mild power of movement; uterus dichotomous, with 15 to 35 branches on each side; may be seen by pressing segment between two glass slides and holding to light (Isaacs reports a method of injecting uterus with India ink); genital pores small, lateral, irregularly alternating. Eggs (embryophore) thick, ovoid, transparent to dark brown; 35–40 microns by 20–30 microns; may be clustered.

HABITAT.—Adult worm known in man only. Infestation usually by only one worm. Cysticercus in cattle, especially in tongue and masseters.

DISTRIBUTION.—Cosmopolitan. Most common tapeworm (Stiles). Very common in tropics, especially in Africa. Common in U. S.

TRANSMISSION.—To man by eating of raw or improperly cooked, infested beef. To cattle through water or forage contaminated by human feces.

DIFFERENTIAL DIAGNOSIS.—From *Tænia solium* (eggs, character of uterus.)

Tænia Solium

(pork-measly tapeworm; armed tapeworm)

MORPHOLOGY.—Two to 8 meters by 5 to 6 mm. Scolex with four cup-like suckers and a rostellum with two rows of hooks (22 to 32). 800 to 900 segments; gravid segments 10 to 12 mm. by 5 mm.; discharged passively in sections of 4 to 6; uterus dichotomous, with 7 to 14 branches on each side; genital pore small, lateral, in irregular alternation. Eggs (embryophore) round, yellowish to dark brown, 31 to 36 microns, may be clustered.

Habitat.—Adult worm known in man only. Infestation usually single. *Cysticercus cellulosæ* in pig and man. Cysts found in males oftener than in females; few to several thousands, ellipsoid, 6–10 mm., most frequently in brain, then eye, muscles, liver, lung, etc.

Distribution.—Wherever man and pig live together. More common in the tropics; comparatively rare in United States and Mohammedan countries.

Transmission.—To pigs, through water or forage contaminated with human feces, or by coprophagy. To man by eating of raw or improperly cooked pork. The oncosphere may arrive in man's stomach by way of hands soiled with his own feces or by reverse peristalsis. The embryo escapes during digestion, bores through the wall, and penetrates to various organs where it encysts and in the course of several weeks forms the *Cysticercus cellulosæ*.

Differential Diagnosis.—From *Tænia saginata* (eggs; character of uterus).

The danger, to the host, of cysticercosis is serious; infestation with *Tænia solium* therefore demands prompt and active treatment.

Tænia Confusa

(*Ward's tapeworm; Ward's Nebraskan tapeworm*)

Morphology.—Eight and one-half meters by 5 mm. Scolex unknown. Segments longer than broad; uterus dichotomous, with 14 to 18 short branches on each side; genital pores irregularly alternating. Eggs oval, thick, striated; 39 by 30 microns.

Habitat.—Adult worm in man. Life cycle not known.

Distribution.—Reported twice in Lincoln, Nebraska.

Tænia Echinococcus

(*echinococcus granulosus; hydatid tapeworm*)

Morphology.—Two and one-half to 6 mm. long. Scolex with 4 suckers and rostellum with two rows of hooks (28 to 500). Three to 4 segments; the first is sterile; the second contains male and female organs; the third is gravid, containing about 500 eggs; uterus shows only lateral knobs, no true branches; genital pores alternate. Eggs ovoid; 30 to 36 microns (not found in man).

Habitat.—Adult worm in dog; occasionally in other carnivora. Cysts in man, sheep, cattle, pig, etc.

Distribution.—The classical home of the echinococcus is Iceland, where it has been estimated that one in every forty-three of the population is infested. It is fairly common in Australia and is found in New Zealand, central Europe, South Africa, Egypt, the Sudan, Argentina. In the United States its occurrence is not rare, but many of the cases are in immigrants.

This is the most dramatic of the tapeworms. The adult worm is among the smallest of the cestodes, though its cysts are by far the largest. It is a particularly villainous parasite, scorning the human intestine as a permanent home, and entering it only to slink away into various organs where it hides secure from medication and even from detection until its slow growth reveals it by very large size or by symptoms of pressure or of obstruction. Even then it is secure from the arts of the internist and yields itself to the surgeon's knife alone.

When ingested, the embryophore is dissolved in the digestive juices, the oncosphere, thus freed, bores through the wall of the tract and comes to rest in various organs. As might be expected, the liver suffers most often. In 1806 cases quoted by Stiles 1011 were in the liver, 147 in the lung and 126 in the kidney. Invasion of the brain is more frequent in children than in adults and in male children than in females. Cysts of the spleen, muscles, pelvic organs, pancreas and spinal cord are by no means unknown; they have been recorded in the bones and the heart. The occurrence of cysts is by good fortune usually not multiple, unless rupture of a cyst has sown the hydatid sand, usually in the peritoneal cavity. Cyst infestation is commonest between the ages of 21 and 40 years and is about equally divided between the sexes.

Having located in an organ the oncosphere develops into a cyst with an outer cuticle and an inner layer of parenchyma, enclosing a cavity filled with fluid; the host contributes an outer connective tissue-pericyst. The cyst enlarges slowly, taking several months to attain the diameter even of one centimeter; but it may eventually grow to the size of a man's head. From the inner parenchymatous wall of the cyst brood capsules may form to the number of several thousands, each capsule eventually coming to contain 10 to 30 or more scolices. Since each of these scolices when transplanted may be the origin of an entirely new cyst, the danger of their dissemination by rupture of the mother cyst or by its puncture for diagnostic purposes (an outworn practice) is evident.

Symptomatology.—The symptoms due to the pressure of hydatid cysts depend upon the localization and are largely those of any slowly growing tumor (pressure, obstruction). In the liver and spleen there is often a primary vicarious hypertrophy of the viscus and later the appearance of the cyst mass, which is rounded, smooth, soft and firm. The so-called hydatid thrill may be present. Pressure of the tumor on the bile capillaries may produce jaundice and on the portal vein and its branches, ascites and a caput medusæ. In the lung there is early hemoptysis; later hemorhage may occur and may be fatal. Pleuritic pain, early dry cough, and dyspnea are usually present. In the brain are noted headache, vertigo, cerebral vomiting, disorders of vision, Jacksonian epilepsy and sometimes thinning of the cranium (X-ray) and localized areas of cranial tenderness to pressure. In any localization there is seldom pain, never temperature, and usually a mild eosinophilia (4 per cent. or more). In case of rupture of a cyst the contained toxic fluid may produce urticaria, cyanosis, dyspnea, and collapse.

Diagnosis.—Diagnosis is not easy, though facilitated in geographical regions known to be infected. The slow growth of the tumor is usually compatible with the maintenance of good general health. Radiographs of lung cysts are frequently characteristic; in the cranium they may show localized pressure atrophy. In fluid available after the rupture of a cyst (sputum, urine, abdominal cavity) scolices, brood capsules, and sugar will usually be found. The complement-fixation test is apparently specific when present. Fairly states that it was positive in

70 out of 83 cases before operation, whereas diagnosis from clinical symptoms alone could be made in only 31.

TREATMENT.—Medicine is useless. Careful surgery offers a good chance of cure in favorable localizations.

Echinococcus Multilocularis

It is possible that this worm may turn out to be a subspecies of *E. granulosus*, and in that case the name should be *E. granulosus multilocularis.*

MORPHOLOGY.—Strobila similar to that of the type form. The cysts produce not only scolices but also immature amœboid embryos, which, having escaped from the mother cyst, may form contiguous daughter cysts or may be carried in blood or lymph to metastatic positions elsewhere. The cysts are apt to degenerate and form the colloid cancers of some writers. Because of the metastatic tendency the malignancy of this type of cyst is marked and the patient eventually succumbs to anemia, emaciation and weakness.

HABITAT.—Adult worm in dogs. Cysts in man, sheep, pigs, but principally in large cattle, somatic occurrence as in type form.

DISTRIBUTION.—Said to be found in South Germany, Switzerland, Austrian Alpine region, Russia, and East Siberia. Said also to be absent from Iceland and Australia.

Hymenolepis Nana

(dwarf tapeworm)

MORPHOLOGY.—Five to 45 mm. by 0.5 to 0.9 mm. It is the smallest tapeworm known in man. Scolex globular and relatively large; rostellum with one ring of 20 to 30 hooks; 100 to 200 segments, breadth greater than length; genital pore on left margin near anterior border of each segment; uterus saclike and when gravid nearly fills the segment. Eggs oval or golobular; 2 distinct membranes; 30 to 60 microns by 16 to 34 microns; oncosphere with mammillate projection at each pole.

HABITAT.—Adult worm in the upper two-thirds of the ileum of man, which is probably the only host; much more common in children than in adults. Rats and mice also are under grave suspicion as being primary hosts. Cysticercus in man (possibly in rats and mice). Several thousand worms may be present in one host.

DISTRIBUTION.—Europe (particularly in Sicily), Egypt, Japan, Siam, North and South America. In the United States it is said to be the second most common cestode found in man.

TRANSMISSION.—In man the egg may hatch soon after oviposition, the embryo then penetrates the wall of an intestinal villus, where it develops the cercocyst. This in turn drops into the intestinal lumen and becomes the adult worm. Because of this mechanism it is possible that a secondary host is not required for the life cycle. If identity with *H. murina* of rats and mice is proved, transmission between them and man may be mutual through infected food and water.

SYMPTOMATOLOGY.—None in mild infections. Where the number of worms is large there may be anorexia, diarrhea, vomiting, convulsions, pruritis ani et nasi, abdominal pain, eosinophilia.

DIAGNOSIS.—The diagnosis rests upon finding the eggs in the stool.

PROPHYLAXIS.—Since transmission may be direct from man to man, infested patients should sleep alone. Stools should be destroyed and bed and underclothing thoroughly disinfected. Care of hands before eating should be scrupulous.

Hymenolepis Diminuta

MORPHOLOGY.—Ten to sixty millimeters by 3 mm. Scolex small and unarmed. 800 to 1300 segments, broader than long; cephalad show yellow spots, each due to a distended receptaculum seminis; uterus incompletely divided; when gravid fills most of the segment; genital pores unilateral. Eggs round or oval; 2 distinct membranes with prominent layer of albuminous substance between; 54 to 86 microns by 25 to 40 microns; may be radially striated; oncosphere with mammil late projection at each pole, often not visible.

HABITAT.—Adult in small intestines of rat, mouse, and man. Rare in man; when found, usually in children. Larvæ in meal, moths earwigs and beetles.

DISTRIBUTION.—North and South America, West Indies, Europe.

Dibothriocephalus Latus

(*broad tapeworm; fish tapeworm*)

MORPHOLOGY.—Up to 9 meters by 20 mm. Scolex elongate almond shaped; unarmed, 2 slitlike suckers. Neck very narrow. 3000 to 42000 segments; breadth 3 to 5 times length, though distal segments nearly square; yellowish gray; uterus with 4 to 6 loops each side of the median line; genital pore single and ventral; segments break loose in chains; posterior may be emptied of eggs; may develop at rate of 30 segments a day. Eggs with an operculum or lid at one end; 68 to 71 microns by 45 to 50 microns; may appear in feces 24 days after infection; hatch in water; similar to eggs of *Diplogonoporus grandis* and *Fasciola hepatica.*

HABITAT.—Adult worm in intestines of man, dog, cat, fox. Plerocercoid in several species of fish.

DISTRIBUTION.—Europe, Asia, Japan. Comparatively rare in North America.

SYMPTOMATOLOGY.—The prolonged presence of *D. latus* in man gives rise to a severe anemia, sometimes simulating pernicious anemia. There may be tachycardia, fever rising at times to 104 degrees, and ocular hemorrhages. The abnormal blood destruction is probably due to a toxin elaborated by the worm, and perhaps liberated only when dead segments are decomposed in the intestine.

TREATMENT.—Removal of the parasite by tæniafuges usually initiates a return to hæmic health.

Diplogonoporus Grandis

(*Japanese double cord tapeworm*)

MORPHOLOGY.—Up to 10 meters by 10 to 25 mm. Scolex unknown. Segments in unknown number; breadth greater than length; uterus rosettiform; genital pores double and ventral. Eggs 63 microns by 48 to 50 microns; thick shelled; with operculum; similar to those of *Dibothriocephalus latus* and *Fasciola hepatica.*

HABITAT AND DISTRIBUTION.—Adult worm has been reported a very few times in intestines of man in Japan and the Philippines. Larva probably in fish.

Dipylidium Caninum

(*Dog tapeworm*)

MORPHOLOGY.—Fifteen to 35 cm. by 1.5 to 3 mm. Scolex with rostellum of 3 to 4 rings of hooks. 80 to 120 segments, 8 to 11 mm. by 1.5 to 3 mm.; elliptic, rather thick; when discharged in feces may resemble cucumber seeds; uterus forms a reticulum; genital pores double, one on each lateral margin. Eggs spherical; 43 to 50 microns; thin shell; produced in clusters of 8–20 in a capsule.

HABITAT.—Adult worm in intestines of dog and cat; occasionally in man, oftenest in children. Larvæ in fleas and lice of dogs and cats, and in *Pulex irritans*.

DISTRIBUTION.—Probably cosmopolitan.

TRANSMISSION.—The proglottids leave the intestinal canal by their own motion, become attached to the hair or fur about the anus and are thence licked off and swallowed by the host or enter the host's parasites, which may in turn be swallowed. Children are probably infected while being licked or "kissed" by dogs.

Davainea Madagascariensis

MORPHOLOGY.—Twenty-five to 30 cm. long. Scolex with rostellum of about 90 hooks. Five hundred to 700 segments; 2 mm. by 1.4 mm.; uterus in loops, at first rolled up nearly into a ball; when gravid, unrolls, filling the segment, and loses its walls; eggs, thus freed, form 300 to 400 clusters in each segment; genital pore single and unilateral. Eggs globular; 8 microns; 2 transparent membranes, the outer terminating in 2 pointed processes.

HABITAT.—Adult worm rare in man's intestines. Secondary host is not known.

DISTRIBUTION.—Found less than a dozen times in tropical Asia, Madagascar and Guiana.

Sparganum Mansoni

(*Manson's larval tapeworm*)

MORPHOLOGY.—Adult worm not known. Larva structureless; 8 to 36 cm. by 1 to 12 cm.; anterior end rounded and provided with two suctorial grooves; may be larger than posterior end; migrates through the body; may cause non-inflammatory subcutaneous tumors; may enter bladder and have to be removed from urethra; has been found in subperitoneal, sub-pleural and connective tissues.

DISTRIBUTION.—Reported from China, Japan, the Philippines, Egypt and Guiana.

Sparganum Proliferum

(*proliferating Japanese tapeworm larva*)

MORPHOLOGY.—Although similar to *S. mansoni*, it differs therefrom in its ability to produce new heads in its periphery.

HABITAT.—The larva is usually found in cysts, which average 1–2 mm. in diameter, situated beneath the skin. Many thousands may be present and in a severe infection the cysts may be widely distributed through the body and may involve the viscera.

A more detailed description of these cestodes as well as of many others, of less importance and not here named, must be sought in the text books of parasitology, some of which are named in the bibliography below.

TREMATODES

The trematodes are ecto- and endo-parasites of very many of the lower animals in a wide geographical distribution; in man they are endo-parasitic only. Human infestation is exceedingly frequent in certain parts of the globe (Asia, Africa) though not to be compared with its wide prevalence in other animals. Since members of only one group (Digenea) are found in man, the descriptions in the following paragraphs will apply to this group alone.

The digenetic trematodes are flat, leaflike organisms, thin or moderately thick, wide or narrow. The surface is frequently finely spinose. The anterior extremity is often conical and always bears the oral sucker, terminal or subterminal, unarmed, in which is the mouth. In only one unimportant species is the second sucker or acetabulum lacking. This lies usually ventrally and a short distance behind the oral sucker; it may be dorsal or terminal, posteriorly. The digestive system consists of mouth, pharynx, blind intestinal ceca, usually (reunited posteriorly in *Schistoma*) but in ***Fasciola hepatica*** and *gigantica* finely dendritic. There is no anus. A nervous system is present. There is a well-defined excretory system, beginning in the so-called "flame" cells and emptying through a cloaca situated posteriorly and usually on the dorsum. All show highly developed genital systems and all except the Schistosomidæ are hermaphroditic. Organs of sense are absent.

The life cycle is complex and involves asexual stages with complete metamorphosis and one or two intermediate hosts. As worked out by Thomas for ***Fasciola hepatica*** it is probably typical. The egg, having reached water, hatches a ciliated, free-swimming miracidium, quite different in appearance from the adult worm. By means of a cephalic boring papilla it forces its way into the second host (usually a snail or mussel) and metamorphoses into a sporocyst, which is essentially a collection of germinal cell masses, each of which goes on to the formation of a redia. The redia is provided with an intestine and a birth pore. It contains germballs from which the larval cercariæ are developed. The curious fact is thus evident that one embryo may produce a number of adult worms. The cercaria is provided with a tail by means of which it swims about until it encysts itself either on plant stems or in a third host, usually a fish. The human host acquires the infection by drinking infested water or by eating raw or improperly cooked snails, mussels, fish and green vegetables (cress, etc.) grown in contaminated water. Since some writers believe that infection may take place directly through the skin (especially with *Schistoma*), wading in infested water must also be incriminated.

Infestation with trematodes is called distomatosis or distomiasis and in the human is found in four almost mutually exclusive forms: hepatic, pulmonary (and cerebral), intestinal, and venal. These are discussed separately below, where it is more convenient to speak of symptomatology.

Diagnosis.—The diagnosis is made almost exclusively on the presence of eggs in feces, urine or sputum, since the physician rarely sees the adult worm except at autopsy. It must be remembered that eggs in the sputum may derive from hepatic flukes as well as from those in the lungs; and in the feces from flukes in lungs and the hemorrhoidal veins as well as in the liver and intestines. The known presence of infestation in the locality in which the suspect is or from which he has come is of service. Though Asia is the great home of human distomiasis, the disease is found in the tropical belt round the world and to a less extent in the temperate zones.

TREATMENT.—The treatment is unsatisfactory and is largely prophylactic at present. Since the parasite does not, fortunately, enjoy long life (probably not over 3–4 years at the most), prevention of reinfection in patients and their removal to regions known to be uninfected, with attention to the general health, may enable them to outwear the disease. Among the drugs male fern, thymol, quinine, etc., have been tried without much success. In schistosomiasis Christopherson reports excellent results—almost specific cures—with intravenous injections of antimony tartrate in sterile salt solution; and Cawston recommends large doses of emetine hydrochloride intramuscularly.

PATHOLOGY.—The pathology is discussed briefly in the paragraphs below.

Hepatic Distomiasis

The worms most commonly found in the liver are *Clornorchis sinensis; Opisthorcis felineus; Fasciola hepatica;* and *Dicrocœlium lanceatum.*

SYMPTOMATOLOGY.—The symptoms of hepatic distomiasis may be lacking, if the infection is light. Usually there is a long series of attacks of diarrhea, often bloody, and increasing in severity and duration. Jaundice is often present and may be intermittent. There are digestive disorders. Slight fever may occur. The liver, and possibly the spleen, is at first enlarged and tender. In constant edema and ascites may occur. The patient may develop a dark, ashen pigmentation, emaciation, weakness and anemia. Death may follow.

PATHOLOGY.—At first there is blocking of the bile capillaries with marked ensuing distension; they may become visible on the surface of the liver. The epithelial lining of the ducts may atrophy, but usually proliferates very actively, producing masses of adenomatous tissue. Later there is cirrhosis and atrophy of the liver tissue.

Clonorchis Sinensis

(*Asiatic liver fluke*)

MORPHOLOGY.—Ten to 20 mm. by 2 to 5 mm., flat, lanceolate, attenuate anteriorly, rounded posteriorly; reddish and nearly transparent when alive; surface smooth. Oral sucker larger than acetabulum. Intestinal ceca well-marked and extend to the posterior extremity. Testes posterior and widely branched. Vitellogene glands not extensive. Egg 27 to 30 microns by 15 to 17 microns; oval; dark brown, with sharply defined operculum; ciliated miracidium present at oviposition; eggs occur to the number of several thousands.

HABITAT.—Gall ducts and, to less extent, pancreatic ducts, duodenum, and stomach of man and cats. Secondary host not determined.

DISTRIBUTION.—Very common in China and Japan, where it is reported in 50 per cent. of some series. Fischer says that 7 per cent. of the native population in Shanghai is infected. Katsurada studied three villages and found over 60 per cent. of infestation. Occasionally imported into the United States.

Fasciola Hepatica

(*common liver fluke*)

MORPHOLOGY.—Eighteen to 51 mm. by 4 to 13 mm.; spinose; pale brown to slate color, and whitish in median zone; cephalic cone; acetabulum larger than oral sucker; ceca very finely dendritic, extending to posterior extremity; vitellogene glands profusely branched, occupying periphery of worm; testes in anterior three-fifths and profusely branched; rosette uterus with numerous coils, frequently visible to the naked eye. Egg 130 to 145 microns by 70 to 90 microns; oval; yellowish-brown; thin shelled; operculated; to be differentiated from eggs of *Dibothriocephalus latus* and *Diplogonoporus grandis;* embryo not present at oviposition. Life history outlined above in the course of general remarks.

HABITAT.—Gall ducts, occasionally lungs and other organs of sheep, where it causes the very important disease of "liver-rot." Also found in cattle, hogs, goats, horses, and other mammals. It is rather uncommon and probably accidental in man; in him it has been reported also in lungs and blood vessels, brain and subcutaneous tissues; but such occurrences are merely clinical curiosities.

DISTRIBUTION.—In the lower animals it is common in Europe and is not rare in North and South America, Asia, Australia, Tasmania and Egypt—in other words, wherever grazing flourishes. Human infestation follows this geographical distribution, but is relatively rare.

In Syria an infection called 'halzoun' results from the eating of raw infected goat's livers. The adult fasciolæ fasten themselves on the mucous membrane of the pharynx, causing vasodilation, swelling, aphonia, dyspnea, perhaps suffocation. It is not rarely fatal.

Opisthorcis Felineus

(*European cat fluke; Siberian liver fluke*)

MORPHOLOGY.—Eight to 13 mm. by 1.25 to 2.5 mm.; lanceolate; reddish; transparent; spineless; suckers of equal size; testes lobate; ceca extend to posterior extremity. Egg 26 to 30 microns by 11 to 15 microns; oval; yellow brown; sharply defined operculum; contains ciliated miracidium at oviposition. Snails and fish are probably secondary hosts.

HABITAT.—Gall ducts of cat, dog, glutton, and man.

DISTRIBUTION.—Europe and Asia. Rare in United States, said to be the most common parasite of man in Tomsk.

Dicrocœlium Lanceatum

(*lancet fluke*)

MORPHOLOGY.—Four to 9 mm. by 2 to 2.4 mm.; lanceolate; spineless; transparent; acetabulum slightly larger than oral sucker; testes anterior to ovary; vitellaria not extensive. Egg 38 to 45 microns by 22 to 30 microns; almost globular; operculum; contain embryo when oviposited. Secondary hosts unknown.

HABITAT.—Gall ducts of cattle, sheep, ass; accidental in men. Other liver flukes known in man are *Fasciola gigantica; Opisthorics noverca; Metorchis truncatum.*

Pulmonary Distomiasis

Only one fluke is found normally in the lung, viz.: *Paragonimus westermanii,* called also Asiatic lung fluke. The disease (paragonimiasis) is known as parasitic or Oriental hemoptysis.

MORPHOLOGY.—Eight to 16 mm. by 4 to 8 mm. by 2 to 5 mm.; pinkish to reddish brown in life; no cephalic cone; broad scale-like spines; acetabulum larger than oral sucker; ceca wide and extend to posterior extremity in zig-zag; vitellaria extensive, marginal, and highly dendritic. Egg 68 to 96 microns by 48 to 60 microns; oval; yellow; operculum; embryo not present at oviposition. Secondary hosts not known.

HABITAT.—Lungs and brain of tiger, cat, dog, hog, man. Very exceptionally found also in liver and vessels.

DISTRIBUTION.—China, Japan, Formosa. Rare in Europe and United States.

SYMPTOMATOLOGY.—The symptoms of lung infestation with this trematode resemble those of chronic fibroid phthisis. There is cough, most urgent in the morning, with tenacious, rusty or bloody sputum, the color of which is in part due to the presence of the eggs, of which as many as 12,000 may be discharged in a day. In serious cases, dyspnea and edema may appear, all symptoms become more persistent, and exhaustion leads to death. In the brain the parasite causes Jacksonian epilepsy.

DIAGNOSIS.—The diagnosis is made almost exclusively on the presence of ova in the sputum. It should be remembered that eggs may be swallowed and discharged in the feces.

TREATMENT.—The treatment is unsatisfactory, as with most of the trematodes. Prevention of reinfection and attention to general health are imperative.

Venal Distomiasis

Three trematodes infest human blood vessels and cause the disease variously named schistosomiasis, bilharziosis, or Egyptian hematuria. They are *Schistosoma hematobium; S. mansoni;* and *S. japonicum.* Unlike all other trematodes, these worms are unisexual, each species having distinct male and female forms. The characteristics of these three trematodes follow.

Schistosoma Hematobium

(*human blood fluke; African blood fluke*)

MORPHOLOGY.—Male: 4 to 15 mm. by 1 mm.; whitish; surface bears numerous small warty spines; intestinal ceca unite behind testes; lateral margins approximated to form the gynecophoric canal, in which lives the female; genital organs confined to small area at anterior end of this canal. Female: 15 to 20 mm.; rolled up—whitish to dark brown, depending on the contents of the intestine; ceca rejoin, as in male; uterus long and contains only a few eggs at a time. Egg 133 to 160 microns by 55 to 66 microns; no operculum; terminal or subterminal spine; no embryo at oviposition.

HABITAT.—Portal veins of man and certain monkeys, migrating to mesenteric and sometimes vesical, uterine, and hemorrhoidal veins. Number in one host varies from very few to several hundred. A snail is the secondary host. Eggs in liver, rectum, and bladder.

Distribution.—Chiefly in Africa; also in Persia, Arabia, India, Panama, Cuba, Porto Rico. Probably cases in United States are imported. Manson estimates that half the population in Egypt are infested.

Schistosoma Mansoni

Very similar to *S. hematobium,* the chief differences being that the ovic spine is lateral and that the genitalia are not involved.

Schistosoma Japonicum

(*Asiatic blood fluke*)

Morphology.—Smaller than *S. hematobium.* Male: 8 to 9 mm. by 0.5 mm.; few spines; otherwise similar to *S. hematobium.* Female: 8 to 26 mm. by 0.4 mm. Egg 83 microns by 62 microns; without spine and operculum; oval; faintly yellow; thick shell; may be mistaken for egg of *Ascaris Lumbricoides.*

Habitat.—Veins of the portal and hemorrhoidal systems in man, cattle, horses, cat, dog, pig. Eggs are found chiefly in the liver and the rectal walls; occasionally in the lung and even in more distant organs; the bladder walls escape.

Distribution.—Japan, China and the Philippines.

Mode of Infection.—The route of infection of these three trematodes was formerly thought to be per ora in contaminated water, but recently Japanese investigators have proved pretty conclusively that the cercariæ enter directly through the skin while the host is wading. The invader makes its way first to the liver and later migrates up the veins against the current to the finer branches of the portal system and its tributaries. Some of the eggs flow back to the liver and are found there, but many are deposited in such a way that they enter the walls of the rectum or bladder, or both, and make their way through to the lumen of the viscus.

Symptomatology.—There seems to be a certain amount of reaction to the initial infection. Passage of the cercariæ (esp. *S. japonicum*) gives rise to pruritus and erythema (called kabure in Japan). About a month later may appear headache, fever, abdominal pain, and diarrhea. Splenomegaly frequently follows invasion of *S. japonicum.* Eosinophilia may be marked (30 per cent. to 70 per cent.). From three months to a year later the localized symptoms appear and are due to irritation from the presence of the eggs. In the bladder the symptoms are dysuria with hematuria at the end of micturition; cystitis; lumbar and pelvic pain. In the rectum they are attacks of diarrhea with mucus and blood and later colicky pain and tenesmus. The rectum may prolapse. In the female there may be inflammation of the cervix and vagina.

Diagnosis.—Diagnosis is made on the basis of the presence of the symptoms mentioned above and of the finding of the eggs in stool and urine.

Treatment.—Treatment has been outlined above.

Pathology.—When the initial febrile stage, due to an acute toxemia, has passed, the chief pathological changes result from the presence of the spine bearing eggs in the tissues. In connective tissue there is an intense round-cell infiltration followed by the formation of granulation and dense fibrous tissue. In the mucosæ there may be ulceration or marked overgrowth of epithelium with the formation of papillomata. On this basis carcinoma or sarcoma sometimes develops.

Intestinal Distomiasis

Trematodes found in the human intestine include *Fasciolopsis buskii; Fasciolopsis rathouisi; Fascioletta iolcana; Heterophyes heterophyes; Watsonius watsoni; Gastrodiscus hominis.* They are rarely reported, although evidence is accumulating that they occur oftener than was formerly supposed. The infestation is limited to Asia, except for imported cases. Symptoms are those of a moderate chronic dysentery. Diagnosis is made on the presence of characteristic ova in the feces.

BIBLIOGRAPHY

BARKER, L. F. The clinical diagnosis of internal diseases. Appleton, 1919.

CASTELLANI AND CHALMERS. Manual of Tropical Medicine. Wm. Wood & Co., New York, 1920.

CAWSTON, F. G. Emetine in bilharzia disease. Jr. Trop. Med., 1922, xxv, 112.

CHRISTOPHERSON, J. B. The successful use of antimony in bilharziosis. Lancet, 1918, 11, 325.

FAIRLEY, N. H. The complement-fixation test for hydatid disease and its value. Med. Jr. Australia, 1922, ix (part 1), 341.

FANTHAM, STEPHENS AND THEOBALD. The animal parasites of man. Wm. Wood & Co., New York, 1920.

HERRERA-VEGAS AND CRANWELL. Hydatid cysts. Nelson's Loose-leaf Living Medicine, 1920.

ISAACS, R. An injection method for aiding in the identification of tapeworm species. Jr. Lab. and Clin. Med., 1921–22, vii, 691.

LEIPER, R. T. Bilharziasis. Nelson's Loose-Leaf Living Medicine, 1920.

MIYAGAWA AND TAKEMOTO. Mode of infection of *Schistosoma japonicum*, etc. Jr. Path. and Bact., Paris, 1921, xxiv, 168.

NARR, F. C. The occurrence of *Hymenolepis nana* infestation in an institute for children. Arch. of Ped., 1919, xxxvi, 639.

NORTHINGTON, J. M. The dwarf tapeworm (*Hymenolepis nana*) as the cause of intestinal symptoms with report of case. So. Med. and Surg. Jour., 1921, lxxxiii, 256.

RANSOM, B. H. The metazoan parasites of man. Nelson's Loose-Leaf Living Medicine, 1920.

RIVAS, D. Human parasitology. W. B. Saunders Co., 1920.

SAVITZ, S. A. Notes on a case of *Dibothriocephalus latus;* diagnosis and treatment. Inter. Clinics, 1920, 1, 98.

STEWART, F. H. *Hymenolepis nana* (Siebold) (the dwarf tapeworm) as a parasite of Indian soldiers. The Indian Med. Gaz., 1916, li, 219.

STILES, C. W. Diseases caused by animal parasites. Modern Medicine, Osler and McCrae, Lea and Febiger, 1914.

——— Illustrated key to the trematode parasites of man. Hygienic Laboratory, Bulletin No. 17, Washington, D. C., August, 1914.

——— Illustrated key to the cestode parasites of man. Hygienic Laboratory, Bulletin No. 25, Washington, D. C., June, 1906.

SECTION III

DISEASES OF THE RESPIRATORY SYSTEM

CHAPTER I

ALLERGIC CORYZA

(*Hay-fever, Pollinosis, Vasomotor Rhinitis*)

BY ROBERT A. COOKE, M.D.

Introduction, p. 481—Etiology, p. 482:—Etiological classification of coryza, acute or chronic, p. 482:—Animal emanations, p. 482; Pollens, p. 483; Sachets and perfumes, p. 483; Foods and drugs, p. 483; Bacterial proteins, p. 483—Symptomatology, p. 483:—Clinical history, p. 483:—Local symptoms, p. 484; General symptoms, p. 484—Physical findings, p. 485; Special findings, p. 485—Diagnosis, p. 485:—Differential diagnosis, p. 485—Complications, p. 486—Association with other diseases, p. 486—Clinical varieties, p. 486:—Pollen coryza, p. 486:—Early form, p. 487; Late form, p. 487—Animal coryza, p. 487; Food and drug coryza, p. 487—Treatment, p. 487:—General measures, p. 487:—Climatic treatment, p. 488—Pollen coryza, p. 488; Coryza from animal emanations, foods and drugs, sachets and perfumes, p. 489—Prognosis, p. 489—Pathology, p. 490—Historical summary, p. 490—Bibliography, p. 490.

Introduction.—In view of the fact that the condition described in this chapter is to be considered from a different point of view than is usual, the term allergic coryza will be used to designate that symptom-complex which arises from a hypersensitiveness of the mucous membrane of the upper respiratory tract and, usually, of the eye. In other words, we are dealing with the well-known subject of hay-fever, but the term hay-fever is only correct when applied to those allergic types caused by pollens. In view of the fact that the term hay-fever has been accepted in medical literature and is so popular among the laity, it need not be altogether abandoned, but can be used to designate the coryza caused by pollens. It is not necessarily limited to the pollen of hay but can include pollens from all sources. Because this so-called hay-fever occurs in two clinical types, we will designate them as early and late hay-fever, corresponding to the so-called spring or rose cold on the one hand, and autumnal catarrh on the other. Pollinosis is a more accurate and scientific term for a case of pollen coryza, and is synonymous with hay-fever. Vasomotor rhinitis is another inaccurate diagnostic term, for it merely expresses a pathological condition for which there is no cause and for which there is no satisfactory treatment. Cases previously diagnosed as vasomotor rhinitis, when properly studied from the allergic point of view, are generally demonstrated to be allergic, and there is therefore good reason for the assumption that all of these cases, not etiologically infective, are truly allergic in character. The term, however, must still be used to designate a pathological condition which is probably due to a state of hypersensitiveness.

Let us now consider all of those conditions in which the clinical manifestations are nasal obstruction, irritation, and discharge accompanied by irritation of the mucous membrane of the eye and pharynx. In view of the fact that we have no word in the medical literature to-day which includes these mucous membranes of the eye and upper respiratory passages as such, the word coryza is used merely to convey a conception, but in no sense to connote a limitation of the disturbance to the nose alone, and it is used because the predominating clinical manifestations are nasal. This condition has been described as a "clinical symptomatic expression of local hypersensitiveness." This definition, although it has been criticized, is perfectly correct in that it is evident that it does not exclude a general hypersensitiveness as well; it merely emphasizes the fact that clinically the manifestations are confined to the upper respiratory tract without any specifications as to the ophthalmic reactions usually associated with it. The fact that cutaneous or even intestinal reactions may occur is of interest scientifically but not clinically.

Etiology.—It is not necessary to rehearse here the proofs of the allergic character of certain types of coryza. This is fully discussed in the chapter on Bronchial Asthma. Because it serves a definite purpose for one attempting the diagnosis of any coryza, an etiological classification has been attempted with reference to all forms, either acute or chronic in character. Since we consider coryza merely as a symptom and are searching for the cause, a satisfactory classification aids us in diagnosis, in differential diagnosis, in prognosis, and in treatment. The following, therefore, is a suggestion to assist in the proper classification of all these cases.

THE ETIOLOGICAL CLASSIFICATION OF CORYZA, ACUTE OR CHRONIC

1. Allergic
    - (*a*) By inhalation
        - Animal emanations
        - Pollens (Hay-fever)
        - Sachets and perfumes
    - (*b*) By ingestion
    - (*c*) By absorption from focus
        - Bacterial proteins
2. Non-allergic
    - Infections
    - Vasomotor rhinitis

This classification has its defects but it will help to group in an etiological way all types of coryza.

Animal Emanations.—The emanations consist of the epithelial scales of all known animals, any of which may give rise to typical attacks in hypersensitive individuals. These constitute from 10 to 15 per cent. of all cases of allergic coryza.

Pollens.—The pollens that are the causative factor of early hay-fever, or rose cold, are those of all of the gramineæ together with the pollens of dandelion, daisy and privet, maple and poplar. These account for at least 95 per cent. of all cases of this type. The pollens acting as causative factors in the late form of hay-fever or autumnal catarrh are ragweed in any of its varieties, goldenrod and other fall flowers. The cases of pollen hypersensitiveness constitute from 70 to 75 per cent. of all the cases of allergic coryza.

Sachets and Perfumes.—Any and all forms of sachet, particularly that in which orris forms the base, are frequently the causes of allergic coryza. As a matter of fact, they constitute from 10 to 15 per cent. of all cases observed.

Foods and Drugs.—While foods and drugs cause all of the typical manifestations of coryza, they always do so in association with other manifestations such as bronchial asthma, urticaria, angioneurotic edema and gastro-intestinal disturbance. No case of a pure uncomplicated coryza has ever yet been observed as due either to food or to drugs, although it is probable that such cases do occur, because of the fact that the coryzal symptoms are present along with other clinical manifestations.

Bacterial Proteins.—These have been included in the classification as causative factors in order to make the classification complete for further study. Reasoning from analogy this seems correct, on account of the fact that in some instances bacterial proteins appear to be the specific cause in other clinical types of allergy, such as bronchial asthma.

Symptomatology.—CLINICAL HISTORY.—Patients presenting symptoms of coryza frequently give a seasonal history. There is one type occurring from the middle of May to the middle of July due to the pollens of grasses, and a late type extending from the middle of August to the middle of October, or to the frost, due to the pollen of ragweed and others of the compositæ family. The season varies slightly, depending upon the location in which the patients live. In those living further south the manifestations, particularly of the early type, are apt to precede those of patients living further north by several weeks, depending upon the time of pollenation of the flora to which they are sensitive. These are the typical cases of hay-fever or pollinosis.

The cases of all other varieties of allergic coryza give an irregular history so far as season is concerned, the attacks depending only upon the presence in their environment of those substances to which they are sensitive. It must also be borne in mind that the history of some patients will be irregular and not distinctly seasonal, even though they may be sensitive to pollens. This occurs under two conditions: (1) where a secondary infection follows the specific allergy and prolongs the season beyond the natural limits of the pollenization itself and appears as a recurrent infection throughout the winter, and (2) where multiple hypersensitiveness exists and the patient is allergic not only to the pollens but to other agents as well. In such cases as this, the unseasonableness of the attack completely confuses the patient, and often the physician, as the clinical history is not typical.

Local Symptoms.—The symptoms of hay-fever are essentially those of a coryza. In some instances they are acute and paroxysmal in type; in other instances the manifestations are so continuous that a chronic condition results.

Sneezing probably always occurs, and in the acute forms is violent and explosive in character and repeated from fifteen to twenty times in succession. In the chronic form it is not so constant a manifestation.

Nasal obstruction usually occurs, due to the edematous condition of the mucous membrane. Where the nares are structurally narrow the obstruction is more or less continuous.

The nasal discharge in the acute cases is thin, watery and excoriating to the skin of the nose and upper lip. It is described as being acid in character and hot and burning. On testing with litmus, however, the discharge is always found to be alkaline. In some cases this discharge is so free that it drips like water from the end of the nose. In the chronic cases this same thin, watery, mucoid discharge may be present. In many cases, both acute and chronic in type, this nasal discharge becomes thicker and often purulent in character, an indication of secondary infection.

Ophthalmic manifestations are also present, and consist in itching and congestion of the conjunctiva and sclera, and of lacrimation. These ophthalmic symptoms vary considerably in their intensity in different cases, and are present in 80 per cent. of the acute cases. In the most severe type edema of the sclera occurs, and is sometimes so intense that the edematous membrane projects between the eyelids. In the chronic type of cases the ophthalmic symptoms are always much less intense but appear to some extent in 50 per cent. of the cases. Photophobia frequently occurs in connection with the acute manifestations.

The posterior nares and pharynx are also frequently involved in both the acute and chronic forms. There is itching, described in many cases as being felt in the ears, and also a discharge from the pharynx and posterior nares. This is usually mucoid in the acute cases, but where the discharge is at all chronic and secondary infections occur, it may be purulent. Cough is commonly an accompanying symptom.

The ears are only secondarily affected as a result of the congestion in the Eustachian tubes. This gives rise to a retraction of the drum membrane, resulting in partial deafness.

Headaches, frontal in character, frequently occur in those cases in which the edema of the nasal mucous membrane causes obstruction with an increased intranasal pressure and a decrease in the aëration of the paranasal sinuses.

General Symptoms.—Fever is occasionally noted, particularly in the acute types. It is rarely higher than 102° or 103° F. (38.88° or 39.44° C.) and lasts only a few days unless secondary infections intervene. Lassitude and depression are commonly present. It is a curious fact that in cases of pollen hay-fever this depression and lassitude are often noted before the actual onset of the paroxysm itself.

Physical Findings.—The mucous membrane of the nose is swollen and edematous. It can be contracted by the use of adrenalin but this effect is only transitory and in some instances no response at all can be elicited. The pharynx is red and congested. In some cases the drum membrane is seen to be retracted. The conjunctival and scleral mucous membranes are congested to a greater or lesser degree.

Special Findings.—For the allergic types of coryza, just as for bronchial asthma, it is axiomatic to assert that the accurate and complete determination of the etiological factors is essential. The special examinations determining these factors consist of the cutaneous and ophthalmic tests which are described under Bronchial Asthma. For purposes of treatment as well as diagnosis the tests must be made with varying dilutions in order to determine not only the allergen or allergens to which the patient is sensitive but to establish the degree of hypersensitiveness, for this varies tremendously in different cases, although the history often gives no indication of this fact.

Cutaneous reactions occur in approximately 90 per cent. of those cases with a typical history of pollen coryza of either the early or the late variety. In a few instances, approximately 3 per cent., the cutaneous reaction does not occur, and in these cases the diagnosis rests upon the appearance of a positive ophthalmic reaction. The remaining 6 per cent. are probably peculiar types of infection occurring seasonally. The *ophthalmic test* is of particular importance, especially when the conjunctival reaction is associated with the nasal reaction, as it demonstrates more conclusively the fact that we are actually dealing with an allergen which can cause the very symptom of which the patient complains.

On the other hand, there are cases of allergic coryza in which ophthalmic reactions are not obtained. In all of these, however, careful questioning of the patient usually elicits the fact that the symptoms are nasal, or nasal and pharyngeal, possibly bronchial as well, but that the eye manifestations are absent. Such instances are rare and do not exceed 3 per cent. of all cases with a typical history.

Diagnosis.—The cutaneous and ophthalmic tests just discussed, the technic of which is described under Bronchial Asthma, form the cornerstone of diagnosis. The postulates formulated there for allergy must be fulfilled in these cases of coryza as well as in those of bronchial asthma. In other words, briefly, it is our duty to show not only that the individual is hypersensitive but that the discovered allergen is the true etiological factor.

Differential Diagnosis.—There are forms of acute and chronic coryza that are clinically identical with the allergic types which form the basis of this article, but can be differentiated from them by the fact that no allergenic substance can be found by careful cutaneous or ophthalmic testings, and also by the positive fact that in these cases infection is often demonstrated in association with foci in the paranasal sinuses.

There is another group, discussed above under Etiology, the so-called vasomotor rhinitis, or nasal neurosis. This is non-infective in character. While not all of these cases have as yet been shown to be allergic, such a considerable percentage of them have now been demonstrated as due to hypersensitiveness that the term "vasomotor rhinitis" should be used only to express a pathological condition, and not to connote a clinical entity.

Complications.—BRONCHIAL ASTHMA.—In 700 cases of allergic coryza asthma was present in 15 per cent. It usually occurs shortly after the onset of the nasal symptoms and is due to an associated hypersensitiveness of the mucous membrane and smooth muscle-fibers of the bronchi.

BRONCHITIS.—In a number of cases in which hypersensitiveness is not present in the bronchi, a secondary infection of the bronchial tubes may occur and lead to prolonged attacks of bronchitis.

PAROXYSMAL COUGH.—Not infrequently, cases of allergic coryza are complicated by a peculiar cough that is difficult to differentiate from pertussis. It is violent and paroxysmal and is frequently accompanied by vomiting. It is due to a hypersensitiveness that has extended to the pharynx and is associated with a marked temporary enlargement of the lingual tonsil. Whether the enlargement of the lingual tonsil is due to secondary infection or to an edema—the result of hypersensitiveness of this tissue—has not as yet been decided.

NASAL INFECTIONS.—In all cases of allergic coryza that are chronic in character infection is bound to occur sooner or later, as the edematous mucous membrane forms a favorable medium for bacterial growth. Sometimes the infection spreads to the paranasal sinuses, in which case the clinical picture becomes that of a suppurative pansinusitis.

POLYPOID DEGENERATION.—This condition of the mucous membrane occurs especially in the chronic cases and is apparently secondary, in most cases, to a suppurative ethmoiditis. In some cases in which no infection has occurred polypoid growths are found, the result of the edematous condition of the membranes produced by the long-standing allergic coryza itself.

Association with Other Diseases.—As has been previously established, 50 per cent. of all cases with any clinical manifestation of human allergy are victims of a multiple hypersensitiveness. Therefore we frequently see cases of allergic coryza associated with eczema, urticaria, angioneurotic edema, and forms of gastro-intestinal disturbance due to foods. All of these conditions are the manifestation of an allergic reaction to some allergen, either food or drug, absorbed by ingestion. In addition to these conditions, bronchial asthma due to some allergen other than that giving rise to the symptoms of coryza is frequently found.

Clinical Varieties.—POLLEN CORYZA.—Pollen coryza, or hay-fever, exists in two forms.

Early Form.—The early form, popularly called rose cold, begins in the middle of May and lasts until the middle of July. It is usually caused by the pollens of grasses, and the symptoms are those described above. It is strictly seasonal, but in some instances the attacks are prolonged beyond the middle of July from one of two causes: either a bacterial infection complicates the condition and prolongs it for several weeks, or the duration of the attack is clinically irregular as a result of other allergic reactions.

Late Form.—The late form of pollen coryza, or autumnal catarrh, begins in the middle of August and lasts until the middle of October, or until frost appears. The attacks are essentially caused by the pollen of ragweed, and the coryzal symptoms are complicated by asthmatic manifestations in 15 per cent. of the cases. In many cases these attacks are not clinically seasonal for the same reasons as those given above under the Early Form.

Combined early and late hay-fever occur in 33 per cent. of all cases. In such instances the attack of the late type is generally the more severe.

These cases are examples of multiple allergic reactions, *i.e.*, they combine both early and late forms of hay-fever. On the other hand, there are cases that are somewhat irregular with reference to the beginning and ending of the season but are seasonal in character. They may be sensitive to some weed or flower whose season is peculiarly prolonged. For example, the daisy flowers from the end of May until late in September, and the same is true of sweet clover. The season for privet and corn is later than for the grasses, as the former do not flower until July. The few cases hypersensitive to these less common pollens give an irregular history of summer disturbance, and the hypersensitiveness to pollens of this group can be demonstrated.

ANIMAL CORYZA.—The victims of this hypersensitiveness give a clinical history of attacks occurring at any time of the year upon exposure to the inciting cause. Where this exposure is intermittent, the attacks are paroxysmal in character. Where the exposure is continuous, the attacks are of necessity chronic in nature. Emanations from any animal or bird may produce this reaction. When these attacks have become chronic, secondary infections usually occur and complicate the clinical picture. Where the infection becomes severe and leads to suppurative sinusitis, this latter condition may entirely obscure the underlying cause.

FOOD AND DRUG CORYZA.—As stated above, uncomplicated cases of coryza from these causes have not as yet been proven. Where the coryzal manifestations are complicated by asthma, urticaria, angioneurotic edema and gastro-intestinal disturbance, it is not unlikely that one of these factors is operative in an allergenic capacity.

Treatment.—GENERAL MEASURES.—The **wearing** of **eye-glasses** and **nasal protectors** serves to relieve some of the symptoms when the exposure is severe and of long duration. The use of **adrenalin** is indicated in a 1:4 dilution of the 1:1000 solution. Its benefits, however, are temporary, and the reaction following its use as eye-drops or nasal spray occasionally produces a condition worse than the former. **Cocain is not advisable** in any except the most extreme cases and should then be used locally by the physician or nurse and never be left to the discretion of the patient.

Climatic Treatment.—There is no place to which the victim of early hay-fever can go for relief except upon the water. The grass pollens are practically universal and cannot be avoided. As far as late hay-fever is concerned, individuals in the Eastern part of the United States get partial relief in the White Mountains or on the coast of Maine, and in Florida. Fortunately this type of trouble does not exist in England or on the continent. It is essentially a disease of the North American continent.

POLLEN CORYZA.—In the treatment of allergic coryza we must always bear in mind the fact that complicating conditions such as hypertrophy of the turbinates, markedly deviated septa, infections of the paranasal sinuses, and polypoid growths, must receive their appropriate treatment in addition to the treatment of the hypersensitiveness itself. In any case that is demonstrably allergic in character these complicating factors should be removed, if possible, before the treatment for the hypersensitiveness is instituted. Such treatment is essentially surgical in character and therefore demands the attention of a rhinologist.

What concerns us most at this time is the specific method of treatment of hypersensitiveness, which may be carried out either prophylactically or phylactically.

(*a*) *Prophylactic treatment* is the most satisfactory as a general thing. Having determined the proper **allergenic substance**, the **injections** should be begun about six weeks before the expected attack. They should be given at approximately weekly intervals from this time until the season is ended. There are a number of preparations on the market which bear the stamp of approval of the Council of Pharmacy and which are put up with specific directions for their administration. The only difficulty with these preparations lies in the fact that they cannot take account of the extreme variations in the hypersensitiveness of the individual and that a more or less rigid system of dosage must be adhered to, which dosage has been determined according to the most sensitive cases. The more sensitive an individual is to a pollen extract, the smaller the dose that can be used and also, as a rule, the better the result obtained.

With regard to the prophylactic treatment, we can say, in general, that in 80 per cent. of the cases 80 per cent. of the trouble is removed. In only 6 per cent. is absolute freedom obtained. Difficulties are encountered in the administration of these extracts. Usually a local reaction is obtained and is of no significance if it does not last over thirty-six hours. In exquisitely sensitive cases, however, care must be taken to avoid over-dosage, as this is followed almost immediately by constitutional manifestations consisting of acute coryza of a severe grade, often associated with a generalized erythema and urticaria, in some few cases with nausea and vomiting; syncope and collapse are rarely induced.

The treatment has to be given each year on account of the fact that the effect lasts but a comparatively short time.

These cases should be tested, preferably, not only for their allergenic reactions but for the degree of their hypersensitiveness, and solutions should be prepared specifically for the individual. In this way better results are obtained.

(*b*) *Phylactic treatment* can be considered in those cases in which the attack has already started. In such cases, small doses are given at first at daily intervals, then at intervals of two, three and four days, the dose and the intervals increasing gradually. In these cases, startling results are often obtained, and on the whole the results are almost as satisfactory as those prophylactically managed, if we consider the results obtained beginning one week after treatment is instituted. Here, too, care must be taken to determine the degree of hypersensitiveness in order to gauge the dosage accurately.

CORYZA FROM ANIMAL EMANATIONS, FOODS AND DRUGS, SACHETS AND PERFUMES.—These may be considered together in treatment. In general it can be said that the cause having been established, the remedy consists in its removal from the patient's environment. In special cases, however, where this cannot be done, satisfactory results are obtained by the **hypodermic injection of the specific allergenic substance.** These injections are given approximately at weekly intervals, and improvement can be noticed after four or five injections. The difficulty with this form of treatment lies in the fact that after freedom from symptoms has been obtained, the injections must be continued at comparatively long intervals, occasionally once a month, in order to maintain this clinical immunity. In cases that have received from fifteen to twenty such injections, it is possible to maintain freedom from symptoms if the patient will expose himself at frequent intervals to the offending substance.

Prognosis.—The prognosis depends upon the etiological factor. Spontaneous cures occasionally occur in any of the types, but at present there is no known determining factor for this phenomenon.

POLLEN CORYZA.—Treatment by injections of pollen extract is indicated except in the case of those patients who can move to a satisfactory environment. Individuals who suffer from attacks of hay-fever and frequently recurring infections of the respiratory tract in the winter often find themselves entirely relieved of the infection after the treatment of their hay-fever with pollen extract alone. The prognosis in cases under treatment by pollen extract is given under Results of Treatment in the chapter on Bronchial Asthma.

OTHER FORMS.—Allergic coryza from all other causes will be relieved entirely upon the removal of all allergens from the environment. In these cases the prognosis is exceptionally good if complicating conditions, such as polypi, receive their appropriate surgical treatment.

Pathology.—ORGANIC.—Less than 30 per cent. of all cases of allergic coryza show structural defects of the nose. Complicating infections are responsible for practically all the organic changes except deviation of the septum. In a few cases with long continued allergic reactions, polypoid degeneration occurs without infection.

FUNCTIONAL.—What is said under Functional Pathology of Asthma in this volume obtains here as well and need therefore not be discussed again.

Historical Summary.—In 1819, John Bostock first described as a clinical entity the seasonal coryza now known as hay-fever or pollinosis. Elliotson, in 1831, was the first to ascribe the attack to pollens. In 1873, C. H. Blackley demonstrated conclusively by experiments upon himself with pollen extract that pollens were the cause of hay-fever. Dunbar was the next to take up a scientific study of the disease and attempt a treatment. His experiments on active immunization of the human were stopped on account of the dangerous reactions obtained. His conception was that the pollen contained a toxalbumin, and he attempted to produce an antitoxin in the horse. On the basis of experiments which demonstrated to him the presence of antitoxin in the serum of an immunized horse, he placed upon the market the preparation known as "Pollantin."

In 1906, Wolff-Eisner suggested that hay-fever was an allergic reaction, and in 1911, Freeman and Noon reported their experiments and the results of treatment with the extracts obtained from the pollens of grasses for the protection of individuals suffering from the early or vernal type of hay-fever. Since 1910 much work has been done along these lines, stimulated largely by the experimental work in anaphylaxis, until now we are able to correlate the numerous forms of coryza from many different causes on the basis of a hypersensitiveness and to appreciate, as well, the correlation that exists between the many different clinical manifestations of hypersensitiveness.

BIBLIOGRAPHY

ANDERSON, J. F. Maternal transmission of immunity to diphtheria toxin. Hyg. Lab. Bull., Washington, 1906, No. 30.

AUER, J. S., AND LEWIS, P. A. Acute anaphylactic death in guinea pigs. Jour. Am. Med. Assn., 1909, liii, 458.

BLACKLEY, C. H. Experimental researches on the causes and nature of hay-fever. London, 1873.

——— New observations on hay-fever. London, 1877.

——— Hay-fever and the pollen of grasses. Brit. Med. Jour., 1898, i. 867.

BOUGHTON, T. H. Kidney lesions in chronic anaphylaxis. Jour. of Immunol., 1916, i, 105.

CLOWES, G. H. A. A preliminary communication on certain specific reactions exhibited by hay-fever cases. Proc. Soc. Exper. Biol. and Med., 1913, x, 69.

COOKE, R. A. Hay-fever and asthma. New York Med. Jour., 1918, cvii, 577.

——— The treatment of hay-fever by active immunization. Laryngoscope, 1915, xxv, 108.

Cooke, R. A. Allergy in drug idiosyncrasy. Jour. Am. Med. Assn., Sept. 6, 1919, lxxiii, 759-60.

Cooke, R. A., and Vander Veer, A. Human sensitization. Jour. Immunol., 1916, i, 201.

Cooke, R. A., Flood, E. P., and Coca, A. F. Hay-fever: the nature of the process and of the mechanism of the alleviating effect of specific treatment. Jour. Immunol., 1917, ii, 217.

Dunbar, W. P. Zur Ursache und spezifischen Heilung des Heufiebers. Deutsch. med. Wchnschr., 1911, xxxvii, 578.

Dünner, L. Die Verwertbarheit der Widal'schen Reaktion bei Schutzgeimpften. Berl. klin. Wchnschr., 1915, lii, 683.

Freeman, J. Further observations on the treatment of hay-fever by hypodermic inoculations of pollen vaccine. Lancet, 1911, ii, 814.

———— Vaccination against hay-fever. *Ibid.*, 1914, i, 1178.

Goodale, J. L. Studies regarding anaphylactic reactions occurring in horse asthma and allied conditions. Ann. Otol. Rhinol. Laryngol., 1914, xxiii, 273.

The diagnosis and management of vasomotor disturbances of the upper air passages. Boston Med. and Surg. Jour., 1916, clxxv, 181.

Preliminary notes on the anaphylactic skin reactions excited in hay-fever subjects by the pollen of various species of plants. *Ibid.*, 1914, clxxi, 695.

Koessler, K. K. The specific treatment of hay-fever (pollen disease). Forchheimer's Therapeusis of internal diseases. 3rd Ed., New York, 1917, Vol. V, p. 665.

Longcope, W. T. The production of experimental nephritis by repeated proteid intoxication. Jour. Exper. Med., 1913, xviii, 678.

———— Susceptibility of man to foreign proteins. Am. Jour. Med. Sc., Philadelphia, 1916, clii, 625.

Meltzer, S. J. Bronchial asthma as a phenomenon of anaphylaxis. Jour. Am. Med. Assn., 1910, lv, 1021.

Noon, L. Prophylactic inoculation against hay-fever. Lancet, 1911, i, 1572.

Oppenheimer, S., and Gottlieb, M. J. The active immunization of hay-fever. New York Med. Jour., 1915, ci, 229.

Otto, R. Das Theobald Smith'sche Phänomen der Serumüberempfindlichkeit. Gedenkschr. f. v. Leuthold, Berlin, 1906, i, 153.

von Pirquet, C., and Schick, B. Die Serumkrankheit. Deuticke, Wien, 1916.

Portier, B., et Richet, C. De l'action anaphylactique de certains venins. Compt. rend. Soc. Biol., Feb. 15, 1902, liv, 170.

Rosenau, M. J., and Anderson, J. F. A study of the cause of sudden death following the injection of serum. Hyg. Lab. Bull., Washington, 1906, No. 29.

———— Studies upon hypersusceptibility and immunity. *Ibid.*, 1907, Washington, No. 36.

Schittenhelm, A., and Weichardt, W. Ueber zelluläre Anaphylaxie. Deutsch. med. Wchnschr., 1911, xxxvii, 867.

Schloss, O. M. A case of allergy to common foods. Am. Jour. Dis. Child., 1912, iii, 341.

———— Allergy to common foods. Tr. Am. Pediat. Soc., 1915, xxvii, 62.

Schloss, O. M., and Worthen, T. W. Permeability of the gastro-enteric tract of infants to undigested protein. Am. Jour. Dis. Child., 1916, xi, 342.

Talbot, F. B. Asthma in children. Boston Med. and Surg. Jour., 1914, clxxi, 708; 1916, clxxv, 191.

Asthma in children: its treatment. Long Island Med. Jour., 1917, xi, 245.

——— Idiosyncrasy to cow's milk: its relation to anaphylaxis. *Ibid.*, 1916, clxxv, 409.

The rôle of food idiosyncrasies in practice. New York State Jour. Med., 1917, xvii, 419.

ULRICH, H. L. Some notes on hay-fever. Jour. Am. Med. Assn., 1918, lxii 1220.

WALKER, I. C. Studies III, IV, V. Jour. Med. Research, 1916-1917, xxxv, n. s., xxx, 487, 497, 509.

——— Studies X, XI, XII. *Ibid.*, 1917, xxxvi, n. s., xxxi, 231.

WALKER, I. C., AND ADKINSON, J. Study I. On Staphylococcus pyogenes aureus, albus and citreus, and on Micrococcus tetragenus and Micrococcus catarrhalis. *Ibid.*, 1917, xxxv, n. s., xxx, 373.

——— Study II. Diphtheroid organism isolated from the sputum of patients with bronchial asthma. *Ibid.*, 391.

Study XIII. The relationship between the cutaneous reaction, serum agglutination tests and bacteriological examination of the sputum and nasal secretions in determining the part Staphylococcus aureus and albus may play in the cause of bronchial asthma. *Ibid.*, 1917, xxxvi, n. s., xxxi, 245.

Study XVI. The sensitization of hay-fever and asthmatic patients to the proteins found in the different parts of plants and to the individual proteins of the cereals. *Ibid.*, 1917, xxxvii, No. 2, n. s., xxxii, 277-285.

Study XVII. A comparison between the cutaneous and the intradermal tests in the sensitization of asthmatics and hay-fever patients. *Ibid.*, 287-306.

WEIL, R. The nature of anaphylaxis, and the relation between anaphylaxis and immunity. Jour. Med. Research, 1913, xxvii, 497.

WELLS, H. G., AND OSBORNE, T. B. The anaphyiactic reaction with so-called proteoses of various seeds. Jour. Infect. Dis., 1915, xvii, 259.

WOLFF-EISNER, A. Das Heufieber, sein Wesen und seine Behandlung, 1910.

CHAPTER II

BRONCHIAL ASTHMA

By Robert A. Cooke, M.D.

Definition, p. 493—Etiology, p. 493:—Allergy, p. 493; Heredity, p. 498; Age, p. 499; General predisposing causes, p. 499—Symptomatology, p. 499:—Clinical history, p. 499; Physical findings, p. 499; Laboratory findings, p. 500; Special findings, p. 501:—Cutaneous test, p. 502; Ophthalmic test, p. 506; Constitutional test, p. 507; Diagnosis, p. 507:—Differential diagnosis, p. 508—Complications, p. 509—Clinical varieties, p. 509—Types, p. 510—Treatment, p. 513: Symptomatic treatment, p. 513; Medicinal treatment, p. 513; Inhalants, p. 513—General measures, p. 514; Specific treatment, p. 514—Prognosis, p. 516—Pathology, p. 516.

Definition.—Bronchial asthma is a condition characterized by dyspnea, both inspiratory and expiratory—especially the latter—due to bronchial spasm and edema of the bronchial mucous membrane. It may be acute or paroxysmal in type, or the condition may be prolonged to such an extent that it becomes subacute or even chronic. The term *bronchial asthma* should be restricted to that condition which is the result of an allergic reaction.

In order to make clear the further discussion of bronchial asthma, the specific terms to be used should be thoroughly understood. The classification suggested by Coca in the chapter on Hypersensitiveness has been adopted as the one that most accurately fulfills our conception today. The word *allergy* is reserved for the reactions occurring in individuals naturally hypersensitive on the absorption of the specific allergen; the word *anaphylaxis* applies to those reactions produced in the human or in the animal after an artificial hypersensitiveness has been brought about.

Etiology.—I. Allergy.—(*a*) *Proofs of Allergic Nature of Bronchial Asthma.*—As a clinical entity, bronchial asthma has long been recognized and differentiated from other types of acute respiratory affections, such as those due to cardiac or renal disease or to tuberculosis. A new and interesting point of view was brought about by experimental studies in protein hypersensitiveness, which began with Richet's observations on animal hypersensitiveness to toxins in 1898, for which he coined the word *anaphylaxis,* and with the accidental discovery by Theobald Smith in 1903 of a peculiar fatal reaction in guinea pigs to a second dose of a serum, not in itself toxic, providing a sufficient time intervened between the first and second injections.

Further studies in this field by Otto, in Ehrlich's laboratory, and by Rosenau and Anderson, established many important facts concerning artificial animal hypersensitiveness to proteins. On the basis of the analogy between these reactions in the animal and certain spontaneous clinical symptoms, Wolff-Eisner, in 1906, suggested the anaphylactic nature of the condition known as *hay-fever,* and Meltzer suggested in 1910 that bronchial asthma as well should be studied in the same light.

The proofs of the allergic nature of bronchial asthma fall under four heads: analogical, experimental, clinical, and therapeutic.

(1) *Analogical.*—In the guinea pig rendered artificially hypersensitive, the reaction that occurs on the introduction of the intoxicating dose is characterized by respiratory distress; in fatal cases death is due to asphyxia caused by bronchial spasm, with the production of a very striking pulmonary emphysema. An eosinophilia is also produced in the experimental animal. Paroxysmal bronchial spasm and eosinophilia are the important clinical manifestations in bronchial asthma—hence the original theoretical deduction that the two conditions were identical and, therefore, that bronchial asthma was also fundamentally anaphylactic.

(2) *Experimental.*—Bronchial asthma, seasonal in character and manifested in conjunction with the well-defined clinical types of so-called hay-fever, has long been recognized as etiologically related to it. Blackley was the first to produce experimentally in himself an attack of hay-fever and asthma by the hypodermic injection of an extract of pollen. Dunbar, attempting to produce an antitoxin in man, found the bronchial and cutaneous reactions so severe in a patient suffering from hay-fever and asthma, that he desisted from its use as too dangerous. It is now a matter of common knowledge that individuals afflicted with horse-asthma should not be given horse serum even in small doses, as used prophylactically against diphtheria. While this is not strictly true, as has been demonstrated, it is a fact that in 50 per cent. of all cases of horse-asthma, the injection of horse serum is followed immediately by the most violent bronchial spasm with dyspnea and in some cases death from asphyxia, exactly as in the experimental animal. It is therefore fair to assume that sudden death in the human, following serum injection, is the result of a hypersensitiveness of the individual, and that the reaction is similar to that observed in the experimental anaphylactic animal.

(3) *Clinical.*—Of 250 consecutive cases of bronchial asthma presenting themselves for the treatment of asthma alone or in association with hay-fever, 214 or 85.6 per cent. gave evidence of hypersensitiveness in a positive intracutaneous test with one or more of the preparations of vegetable or animal emanations or foods.

(4) *Therapeutic.*—To further substantiate the thesis that a certain percentage of the cases of bronchial asthma are demonstrably allergic in nature, it can be stated that of 107 cases with a history of horse-asthma, 105 gave positive cutaneous reactions to a solution of the proteins of horse dander. Forty-five of this group were so sensitive

that moderate exposure to the horse invariably provoked an immediate asthmatic attack. Therapeutic injections of the protein solution in these cases were followed by a freedom from asthmatic manifestation, even after prolonged and intimate exposure to the animal.

These then are the most important positive reasons for the acceptance of the allergic reaction as the basis of that clinical condition known as bronchial asthma. We have no other explanation that is so fully and completely satisfactory. The cumulative evidence of all observers during the past ten years is overwhelmingly in favor of hypersensitiveness as the basic factor in asthma.

In view of the fact that allergy plays so important a rôle in bronchial asthma, it seems necessary to state here that the 250 cases which form the basis of this article have been studied particularly from this standpoint. All cases are tested by means of the intradermal or ophthalmic reactions or both. Solutions for testing are prepared from pollens, sachets, animal emanations, foods, and drugs.

Although we speak generally of *protein* hypersensitiveness, it must be borne in mind that the natural hypersensitiveness as seen in the human may be to chemical substances or molecules not protein in nature. For example, there are definite cases of a hypersensitiveness to glue. The individual sensitive to this substance will develop symptoms of edema of the tongue and lips on moistening a postage stamp and, in one instance, this sensitiveness was so extreme that an open bottle of glue in a room was enough to give rise to symptoms of asthma and hay-fever in from ten to fifteen minutes if the person was within fifteen feet of it. Such cases belong in the same group as the cases of protein hypersensitiveness, as will be shown later, both by their hereditary history and by the cutaneous reactions to non-protein substances. The drug idiosyncrasies are also allergic in nature. These will be discussed more in detail later but are mentioned here to show the wide range of study and the variety of tests necessary before pronouncing any case non-allergic in nature.

(*b*) *Classification of Asthma.*—As a result of the studies made it has seemed wise to adopt an etiological classification of asthma based upon the allergic or non-allergic nature of the chief complaint, paroxysmal dyspnea.

1. Allergic	
(*a*) By inhalation	Animal dander Pollens Sachets and perfumes
(*b*) By ingestion	Drugs Foods
(*c*) By absorption from focus	Bacterial proteins
(*d*) By subcutaneous or intravenous injection	Therapeutic sera

2. Non-allergic
    - Chronic bronchitis and emphysema
    - Tuberculosis, pulmonary
    - Cardiorenal disease
    - Thymic enlargement
    - Enlarged bronchial glands
    - Reflex bronchospasm
    - Acute bronchitis

Like all classifications this one has its distinct limitations, and yet it serves a purpose in that it gives a definite ground work for proper and accurate diagnosis, differential diagnosis, prognosis, and treatment. In other words, we must consider bronchial asthma, acute or chronic, merely as a symptom, the manifestation of a spontaneous hypersensitiveness to some chemical substance absorbed by the individual, or as a symptom induced by one of the non-allergic causes above enumerated. Under Allergic Causes (p. 495) an attempt is made to enumerate not only the basic etiological factors but also the path of absorption through which they usually reach the susceptible individual. It must be appreciated that this is not invariably the rule. For example, an individual who was exquisitely sensitive to horse serum gave a history of a severe allergic reaction on subcutaneous injection of the serum in the form of diphtheria antitoxin eight years previously. Cutaneous and ophthalmic reactions were markedly positive. The inhalation of a minute amount of powdered horse serum gave just as immediate a reaction, with symptoms of hay-fever and asthma. Another case, a child, gave a history of acute egg-poisoning. The ingestion of the most minute amounts of egg-white was immediately followed by tingling and swelling of the tongue and fauces, swelling of the nasal mucous membrane and watery nasal discharge, cough and dyspnea. If a sufficient amount was taken, vomiting and, later, urticaria developed. This child gave prompt and marked cutaneous and ophthalmic reactions to the test. The inhalation of a minute amount of powdered egg-white gave the same reaction.

These cases simply illustrate the fact that it is the allergenic substance itself, no matter how introduced, that produces the symptoms; but the classification is none the less helpful in that it specifies the usual channel of absorption. The bacterial proteins absorbed from foci of infection have been classified under Allergic Causes (p. 495). Walker, using soluble bacterial proteins, was able to demonstrate a hypersensitiveness by the skin reaction in patients with bronchial asthma, but there is still considerable difficulty in demonstrating the fact that bacteria cause bronchial asthma by strictly allergic reactions.

(*c*) *Underlying Principles Postulated.*—In view of the fact that the study of bronchial asthma from the allergic point of view is so new, and also because so much is being written to-day by so many different observers, it seems necessary here to interpose a word of caution. In order that our studies may not become confused by a mass of unimportant statements of findings regarding the etiology of asthma, it is essential to lay down certain postulates that must be fulfilled before one may assume or prove that any protein, or other chemical substance, is etiologically important in a case of hypersensitiveness. The allergic condition of any individual is then placed on a sound and definite basis.

1. Sensitization must be demonstrated by one of the following:
    (*a*) A positive local reaction, cutaneous or ophthalmic.
    (*b*) The original allergic manifestation must be artificially reproduced at will on introduction of the substance, either inhaled, ingested or subcutaneously injected.
2. It must be shown that the individual has come in contact in some way with the suspected substance in order to permit it to act as an etiological factor.

When these postulates have been fulfilled in any case, then treatment, instituted accordingly, is placed upon a safe and accurate basis in agreement with the contention for an allergic reaction.

As far as the pollens, animal emanations, sachets, drugs and foods are concerned, these postulates are readily fulfilled in any individual case. But for the bacterial proteins this is not so, except in a very small percentage of cases. Walker, in his study of this phase of allergy, concludes that there is no correlation between the cutaneous reaction, the agglutinin or precipitin tests, and the recovery of the organism on culture. In view of this it is impossible to understand the satisfactory results of his vaccine therapy. They cannot be interpreted in the light of our present knowledge of allergy but must rather be attributed to some form of non-specific immunity. It seems wiser, therefore, for the present to place those cases of bronchial asthma apparently due to or complicated by chronic nasal and bronchial infections in the non-allergic class, reserving as well a division in the etiological classification for the bacterial proteins in cases where the postulates are fulfilled. As stated above, these constitute a very small percentage, but they do occur, as is illustrated by the following case:

A patient, 41 years of age, had suffered from asthma for 30 years, following an attack of whooping-cough. Attacks were very frequent, every two or three weeks, except for the last two years before examination, when they had been practically continuous. For a few weeks there had been a slight afternoon temperature. Cough and a slight mucoid expectoration were constantly present. Proper physical, laboratory and *x*-ray examinations for tuberculosis were negative. The leukocyte count was 8,600 and an eosinophilia of 11 per cent. was found. Special examination by the intracutaneous tests gave negative results with all foods except lobster, which was never eaten. The preparation of chicken feathers yielded a moderately positive reaction. The rest of the animal emanations, sachets and pollens were negative. Every article containing feathers was removed from the environment with no effect upon the asthma whatsoever. A culture of the sputum showed *Streptococcus viridans* and *hemolyticus*, and the bacillus of influenza.

A positive cutaneous reaction to these bacteria was obtained. They were incorporated in a vaccine, 1.5 billion of the streptococci in equal parts, and one billion influenza bacilli to each c.c. Injections of 1/10 c.c. of this vaccine regularly produced marked exacerbation of the asthma for 24 hours after each of the first injections. Later injections produced no reaction of a local or constitutional nature until twelve injections had been given, the last amounting to 0.6 c.c. at weekly intervals. After the third injection definite improvement began and the patient has been free of all attacks for a period of six months.

II. HEREDITY.—In an article written jointly with Vander Veer, certain factors regarding the inheritance of human hypersensitiveness were discussed, and only the conclusions need be enumerated here.

(1) Allergy with clinical manifestations exists in approximately 10 per cent. of all human beings.

(2) Over 48 per cent. of cases with clinical hypersensitiveness give a positive family history in contrast to only 14.5 per cent. of cases showing a positive antecedent history in apparently normal individuals.

(3) Inheritance exerts a definite effect upon the age at which symptoms appear. The closer the relationship and the more complete, the earlier is the manifestation. In other words, where the inheritance factor is derived from both paternal and maternal sides the period of maximum liability is in the first five years, when 36.3 per cent. develop manifestations. On the other hand, where the inheritance is paternal or maternal and not both, the height of the incidence curve is reached between the ages of ten and fifteen years; in those cases in which no history of inheritance is given and in which, therefore, it is presumably more distant, the onset curve does not reach its maximum until the age of from twenty to twenty-five years.

(4) Regarding the nature of the inheritance, it may be definitely stated that there is no transmission of the specific clinical hypersensitiveness from parent to child. This opinion is substantiated by the fact that the offspring of allergic individuals are not born allergic. A comparison of the clinical manifestation of antecedent and descendant also shows that they are more frequently different than similar. This was particularly well illustrated by the histories of six pairs of twins in which the twins manifested the same allergic reaction in three pairs but in which hypersensitiveness was absent in one, though present in another, in three pairs; in only one instance was the hypersensitiveness identical with that of the forebear.

(5) It has also been possible to show by a study of a large group of cases that the hypersensitiveness was apparently transmitted from antecedent to descendant according to the Mendelian law and that it is a dominant characteristic.

To sum up, inheritance plays a definite rôle by transmitting to the descendant not the hypersensitiveness itself, but a peculiar tendency toward abnormal bioplastic activity of the body-cells.

III. AGE.—This factor has been discussed briefly under Heredity.

The age of onset depends entirely upon the antecedent history. Apparently no age is immune, for definite records show that clinical manifestations have appeared as early as the first few days of life and in one case as late as the sixty-ninth year. The age of maximum liability, disregarding all inheritance, is from about five to twenty-five years.

IV. General Predisposing Causes.—Almost all cases of bronchial asthma of any long standing give as the apparent reason for attacks a large and heterogeneous group of causes,such as cold, dampness, extreme altitude, over-exertion, nervous or physical fatigue, over-eating, and exposure to certain irritating vapors, fumes or dust. It is an important fact that these causes are not operative in the early development of the disease. Apparently they act only in those individuals in whom bronchospasm has become a habit as a result of some previously manifested allergic reaction. For example, individuals who have had horse-asthma for a number of years react, at first, only upon exposure to this particular animal. The intervals are free and clear. After a sufficient number of these specific attacks have occurred, however, the attacks begin to occur irregularly without any exposure to horse, and are ascribed to some of the various reasons above enumerated. The only satisfactory explanation for this is that the bronchial mucous membrane and smooth muscle-fibers of the bronchi have acquired the habit of reactivity and that they manifest this upon the slightest provocation from any irritation. These cases, when treated for the specific reaction, soon become able to withstand all of the non-specific factors. This is the best proof of the fact that the latter are to be considered in no sense as fundamental causes.

Symptomatology.—Clinical History.—*Dyspnea.*—The acute paroxysms of bronchial asthma are made manifest by a dyspnea that is both inspiratory and expiratory in character, though the expiratory phase is the more pronounced and is distinctly and definitely prolonged. During this period of dyspnea the patient complains also of wheezing, and this may be so extreme that it can be heard at a distance of from twenty to thirty feet. At times the wheezing is loud and bubbling in character, and at other times, in which there is little exudate in the bronchi, it may be merely of a peculiarly harsh character.

Cough.—This is usually present together with expectoration. The expectoration in bronchial asthma is somewhat characteristic. In the acute and paroxysmal types there is little at first, but later a peculiar gluey, stringy mucus, the so-called Cushman's spirals, may be raised. In those cases in which a secondary infection occurs the expectoration may become distinctly purulent in character. With the cessation of the attack the sputum is raised freely, with considerable relief to the patient.

Pain.—This is never of the type of a pleuritic pain, but is due to the extreme muscular exertion, the result of the bronchial spasm. It is therefore general, and may affect the muscles of the back or the diaphragm, or the accessory respiratory muscles of the neck.

PHYSICAL FINDINGS.—*Posture.*—The posture of the patient in the midst of an asthmatic attack is fairly characteristic. He sits upright in bed, or preferably in a chair, supporting his elbows at a slight elevation in order to aid the accessory muscles of respiration. The breathing is seen to be labored; the expiratory phase of respiration is markedly prolonged and the wheezing can be heard at a distance.

Chest.—The expansion is poor, the chest being for the most part in a condition of inspiration. Palpation yields no definite information, except that in many cases the bubbling râles can be distinctly felt through the chest-wall. On percussion there is marked increase in the pulmonary resonance over the entire chest; in severe cases even a dull tympany can be elicited. This is due to the associated emphysema. Cardiac dullness may even be obliterated on account of this emphysema.

On auscultation, râles may be heard throughout the entire chest, coarse, mucous, bubbling, or fine and subcrepitant in character, together with sibilant and sonorous sounds. This has been well described as "a music-box chest."

General Symptoms.—A complete and careful physical examination, covering eyes, ears, nose, throat, superficial nodes, heart, abdomen, skin and reflexes should always be made in order to eliminate those other conditions which may produce apparently typical attacks of true bronchial asthma, or even be associated with it and require medical attention.

LABORATORY FINDINGS.—*Sputum.*—The appearance of the sputum in cases of acute paroxysmal bronchial asthma is characteristic. It is composed of fine mucoid shreds which under the microscope have a peculiar spiral form and are known as Cushman's spirals. The Charcot-Leyden crystals are also frequently present, and on staining many eosinophil cells are seen. The significance of the spirals and crystals is not known. The eosinophilia, however, is somewhat characteristic of the disease and has the same significance in the sputum as it has in the blood.

Blood.—The leukocyte count, hemoglobin, and red blood-cells are normal unless there is interference by some concurrent disease.

The differential blood-count is, however, in certain cases characteristic, in that there is an eosinophilia. An eosinophilia can be artificially produced in animals by the injection of foreign proteins. Whether or not this depends upon the kind of protein or whether it depends upon some special reaction has not been determined. Certain it is that not all forms of protein will, in the quantity in which they have been used, produce any eosinophilia in the human. For example, in the hay-fever cases an eosinophilia is the exception, not the rule, and injections of pollen proteins do not produce an eosinophilic reaction. The same may be said for certain definite well-defined cases of natural hypersensitiveness to other proteins. To illustrate: A man with a history of horse-asthma and who suffered from attacks of asthma had an eosinophil count of 2.7 per cent. After he had received seven injections of the protein of horse-dander and the symptoms were relieved, the eosinophil count remained the same.

Of the 250 cases which form the basis of this study differential counts were made in 90 cases. Of these, 69 were proven by cutaneous reactions to be typically allergic in nature, and of these 69 cases 46, or 66 per cent., showed an eosinophil count of over 4 per cent. On the other hand, 21 of these 90 cases were not shown by any tests to be allergic. Of these 21 cases 10, or 47 per cent., showed an eosinophilia of over 4 per cent. The cases are too few and the difference in the percentages is too small to warrant our placing too great reliance upon the differential count. In all of these 21 cases foci of infection were present in the form either of a chronic bronchial infection or of chronic nasal sinusitis, and it may be that in these cases the increase in the eosinophils is due to a hypersensitiveness to bacterial protein. As has been mentioned before, the rôle that these play in true allergic reaction is still uncertain and therefore does not permit of an accurate interpretation. But in contrast to normal individuals we see in all cases of bronchial asthma, either allergic or infective in nature, a definite increase in 62 per cent., that is, in a total of 56 cases, of the 90 in which the counts were made. In all of the cases studied where an eosinophilia was present other causes for this, such as intestinal parasites, were excluded by proper examination.

In short, then, it may be stated that eosinophilia is to be found in approximately two-thirds of all the cases of bronchial asthma. The interpretation of this finding, however, must depend upon the future, for, as has been shown, it is not entirely dependent upon the introduction of an allergen.

Blood-pressure.—A distinction must be drawn between observations made during and between attacks. Between the attacks the blood-pressure, both systolic and diastolic, is frequently low. It is not uncommon to find systolic pressure below 100, and diastolic as low as 50 mm. of mercury. When the readings are made during a paroxysm the systolic pressure is usually elevated, and this is due to the extraordinary efforts at respiration. In one instance in which the systolic pressure between attacks was 95 mm., during an attack the systolic pressure was read at 160 mm. That this is not a true hypertension, however, is shown by the fact that the diastolic readings do not vary to anything like the same extent. In the instance above mentioned, a diastolic pressure of 45 mm. between attacks was only elevated to 60 mm.

A further confirmation of the fact that this increase in systolic pressure is due to respiratory effort is shown by the readings made during an attack prior to an injection of adrenalin, and again within five minutes after the injection, when the dyspneic effort had ceased. Before adrenalin was given, the systolic pressure was 160. Five minutes after the injection of 15 minims (0.92 c.c.) of a 1/1000 solution the systolic pressure had fallen to 120 mm., and this in spite of the fact that adrenalin is supposed to increase blood-pressure. This statement has been substantiated in a number of observations.

SPECIAL FINDINGS.—The testing of patients with suspected allergic conditions, for the determination of their hypersensitiveness, is the essential and important part of our present-day study of bronchial asthma.

For some reason as yet unknown, individuals, whose clinical reaction to an allergen is manifested in the upper respiratory tract or the bronchial tree, show at the same time a hypersensitiveness of the epithelial cells; this fact is made use of in the tests. The substance or substances to be tested are made up in solution, the special method of preparation being somewhat different in each case, depending upon the chemical constitution of the molecule; in general, saline, or very weakly acid or alkaline solvents are used, or very dilute alcohol. It is essential that the solution be non-irritative to the normal individual. All of these solutions are extremely dilute. They are standardized either by weight or by nitrogen content. The latter method is by far the more accurate.

The weakest pollen solution used in making tests contains 0.001 mg. nitrogen per c.c., and the maximum solution 0.3 mg. per c.c. The latter solution, however, is so strong that its use is rarely to be recommended.

There are three methods by which hypersensitiveness can be determined:

I. *Cutaneous Test.*—This test may be carried out either by scarification, or, on the other hand, by the introduction of the above solution into the superficial layers of the skin by means of a hypodermic needle. Both methods have their advantages. When the scarification method is used, only the most superficial layers of the cuticle are removed and the dried substance, or a solution of the substance to be tested, is applied directly. The intracutaneous test is best performed by means of a hypodermic syringe, using a fine needle, preferably a 26 gauge; the needle is introduced into the most superficial layers and an amount not exceeding 0.01 of a c.c. is introduced. This in itself forms a small papule approximately two mm. in diameter.

In either case, a number of tests can be done at one time, using the arm or forearm after it is thoroughly cleansed with alcohol. It is a comparatively simple matter to make as many as thirty tests at a time if proper precautions are taken. These precautions will be elaborated later.

The advocates of the scarification method claim that it has an advantage in that it is more specific; but the reason for the greater specificity is that certain substances do not react by this method whereas a reaction is shown by the intracutaneous test. They contend that the intracutaneous test is therefore too delicate and is not a proper index for treatment. The advantages of the intracutaneous test are that it is the most delicate test made and gives the greatest number of definitely positive reactions for the reason that it brings the solution into more intimate contact with the cells. As a matter of fact, when properly done it does not reach any deeper layer of cells than those exposed by scarification. The intracutaneous test is much less painful than the scarification, and it is as easy of interpretation, with reference to treatment.

In determining the cutaneous hypersensitiveness of any patient we first attempt to determine all the possible reacting substances within our ken at the time. Those reacting positively can then be studied more carefully, using dilutions, and determining the point at which the reaction does or does not occur. As far as the gauging of treatment is concerned it can be stated that individuals reacting to the most dilute solutions show an exquisite degree of sensitization, and that the early dosage must be regulated accordingly.

(*a*) *Interpretation.*—In negative tests there is little or no increase in the size of the original papule, no surrounding zone of hyperemia and no subjective itching.

The positive tests are graded as marked, moderate or slight, using three, two and one plus signs respectively.

(1) *The markedly positive reaction* appears within from five to fifteen minutes after the test is made. There is a considerable increase in the size of the papule and an urticarial wheal is developed, sometimes from two to three c.c. in diameter with pseudopodlike projections out into a surrounding zone of hyperemia; itching is usually an accompanying manifestation. This reaction usually disappears within twelve hours. In exquisitely allergic individuals in whom the test has been made low down on the forearm a typical acute lymphangitis is frequently developed, extending to the axilla, with swelling, pain, and tenderness in the axillary glands. This lymphangitis is much more rapid of development than that ever observed in an infection, for it frequently manifests itself within five minutes of the time the test is made. This shows that the lymphatic vessels are also peculiarly affected in an allergic individual.

(2) *Moderately positive reactions* show the surrounding zone of hyperemia, and there is a certain increase in the size of the wheal, but the pseudopodia are absent. Itching is sometimes present but is more apt to be absent. This reaction disappears as a rule in twelve hours.

(3) *The slight reaction* is merely a lesser grade of the moderate one, with hyperemia and a slight increase in the wheal.

(4) *Doubtful or pseudo-reactions* occur that are difficult of interpretation. Certain individuals develop a hyperemia and show a tendency toward wheal-formation on the introduction of mere saline into the skin; by the scarification method these same cases show a wheal simply from the mechanical irritation of the instrument. A control test must always be done, and if a test solution shows no more reaction than the control it should of course be considered negative. But in this type of case where there is a greater reaction than with the control, it can be concluded that the test is positive. Irritative reactions are commonly met with in those asthmatics who show at the same time a *tache cérébrale.*

(5) *Delayed reactions* occur in some cases. There is no appearance of activity at the site of the test for an hour, but when the individual is seen at the end of twenty-four hours, or even forty-eight hours, there is a definite zone of hyperemia with an accompanying edema—not a true urticarial wheal. The interpretation of these delayed reactions is very difficult and the chances are that they designate a true cutaneous hypersensitiveness in a mild form.

In testing individuals for hypersensitiveness care must be taken not to make too many tests at the same time. Where there is marked positive reaction to several different proteins at one and the same time there is apt to be an uncomfortable constitutional manifestation, apparently the result of the sum total of all the reactions. As mentioned above, at least thirty tests can be made at the same time but only four or five simultaneously, and five or ten minutes should be allowed to elapse before this procedure is repeated; in that time it will be apparent which, if any, of the tests are going to show a marked positive reaction.

(*b*) *Value of the Cutaneous Reaction.*—In general it may be stated that the cutaneous reaction is the principal asset in the diagnosis of allergic conditions and hence the chief indication for treatment. It is not, however, positive in 100 per cent. of all cases giving clinical manifestations to some chemical substance. It can practically always be relied upon in such conditions as hypersensitiveness to animal dander and pollen. There are less than 2 per cent. of all cases with typical histories in which it has not been of positive value. A case of supposed horse-asthma in which the test was negative was exposed to horse without any clinical reaction. The test with timothy pollen was positive and the attacks that had followed exposure to horses in the barn were found to have been due, not to the dander of horses but to the pollen of the hay.

On the other hand, there are cases in which a true clinical allergic reaction occurs from some allergen, but in which the hypersensitiveness is strictly limited to some organ or organs, such as the stomach or bronchi, and is not associated in any way with a cutaneous hypersensitiveness to the same allergen. It has been doubted by some that this condition of localized hypersensitiveness can exist, and some observers have stated that no local manifestation of hypersensibility can occur without the background of a general hypersensibility. This, however, is not a fact, and the surprising thing is that the cutaneous reaction is positive in such an enormous percentage of cases. To illustrate the fact that strictly localized hypersensitiveness does occur with negative cutaneous reactions, the following case may be cited in which the ingestion of clams was always promptly followed within from one-half to one hour by abdominal pain, cramp-like in character, by nausea and later, by vomiting and diarrhea. The cutaneous reaction to the test, however, has always been negative. The assumption in such a case must be that the hypersensitiveness is, for some unknown reason, limited to the mucous membrane and smooth muscle-fibers of the stomach and intestinal tract.

Another case may be cited which illustrates the negative cutaneous reaction in allergic conditions, and also illustrates how our postulates for anaphylaxis can be satisfied by means of the constitutional reaction. The patient, a woman forty years of age, who had never before exhibited symptoms, suffered three violent attacks within three months, characterized by dyspnea so severe that asphyxiation was induced and she became unconscious. This coma lasted for about six hours and was followed by a persistent and intense hacking cough and by nausea. There was no vomiting and no fever. Physical examination at the time of attack showed nothing abnormal, although the eosinophil count was 10 per cent. The cutaneous reactions were negative to pollens, animal emanations, sachets, and to foods, with the exception of lobster, which she had not eaten and with which she had not come in contact at all at the time of these attacks. On careful questioning it was discovered that she had been given some capsules to prevent a cold, and as near as she could recollect had taken two or three of these capsules before each one of her attacks. The capsules contained aspirin, quinin and strychnin. Both the aspirin and quinin cutaneous tests were made and, without there being the slightest indication of a positive cutaneous reaction, in about ten minutes after the tests the peculiar, frequent, hacking cough, tingling and sense of stiffness of the tongue, a feeling of fullness and tension in the chest developed, together with considerable respiratory distress. This passed over in the course of half an hour. On another day the test with aspirin alone was done and the same symptoms were manifested in the same length of time. The following day quinin was tested; the cutaneous reaction was negative and there were no constitutional manifestations. At a later time the aspirin test was repeated with identical results.

It must also be said, on the other hand, that there are markedly positive cutaneous reactions which are not verified by clinical allergic manifestations. Longcope has mentioned this fact, and his observations have been thoroughly substantiated. The lack of clinical manifestations in such cases, however, must be attributed to the fact that the reacting substance is never, in the ordinary course of events, brought into intimate contact with the sensitized cells themselves. This can be illustrated briefly by the incident of a patient who gave a positive cutaneous reaction to the protein of beef, but who never suffered from urticaria, from eczema, nor from any of the conditions which are theoretically ascribed to allergy. The absence of clinical manifestations is due to the fact that the intestinal tract of this individual is not hypersensitive to this protein, and that beef is properly digested and split before absorption in such a way that the protein as such never comes in contact with the cutaneous cells. But the patient is what we may well call potentially allergic and, under the proper conditions, some evidence would manifest itself clinically.

Another case illustrates this same point and also explains what is meant by the term "potentially allergic." This patient gave marked positive reaction to the pollen of ragweed, although he had never had the slightest manifestation of autumnal hay-fever up to the age of thirty-five. It is interesting to note that in this case the ophthalmic tests were negative with the strongest pollen solutions. Two years later he developed autumnal hay-fever in a mild form, and had it severely the following year. At this time the cutaneous reaction was the same but the ophthalmic test showed an exquisitely hypersensitive conjunctiva. This, however, does not hold for all cases, and it is impossible to foretell which patients will develop one form or another of allergy at some time during their lives. As a rule it can be said that the cases that have shown definite allergic manifestations for a very short time and have perhaps suffered for only one or two seasons from such a condition as hay-fever, will fail to show any cutaneous reaction, or that possibly the reaction will be only slight or moderate with the strongest solutions, while the ophthalmic reaction shows an exquisite degree of hypersensitiveness.

II. *Ophthalmic Test.*—Another method of determining hypersensitiveness is by means of the ophthalmic test. It is extremely simple. A drop of the solution of the substance to be tested is placed on the conjunctiva. The reaction that ensues, if any does ensue, varies in intensity from very slight to most severe, depending upon the strength of the solution used and the sensitiveness of the individual tested.

This test can be applied for determining not only hypersensitiveness, but also the degree of the hypersensitiveness. In those cases in which it is marked there is an almost immediate injection of the cornea and conjunctiva, with lacrimation, and intense itching. Nasal symptoms frequently develop when the solution has been carried through the nasal duct; these consist of sneezing, watery discharge, and swelling of the mucous membrane, limited to that side of the nose on which the ophthalmic test has been made. Very slight reactions consist of swelling and redness of the caruncle with some injection of the conjunctiva itself, usually with the dilatation of a few corneal vessels just below the iris.

This ophthalmic test is of particular importance in cases of allergic coryza with or without bronchial asthma. It is occasionally positive in these cases when the cutaneous tests are negative. In cases of true pollen coryza it is present in 95 per cent. It is also present in certain cases of hypersensitiveness to foods, especially those in which the clinical symptoms, caused by the ingestion of the specific allergen, include associated nasal and ophthalmic manifestations. It is more apt to be associated with hypersensitiveness to foods as seen in children, especially when egg-white is the allergic substance. In the few cases of pollen hypersensitiveness in which the ophthalmic reaction is not positive, the clinical history regularly shows an absence of ophthalmic manifestations, and in these cases it is possible to demonstrate nasal reactions after instillation of pollen extract into the eye with a total absence of ocular manifestations.

III. *Constitutional Test.*—Special study of those cases of allergy that have shown no reaction by cutaneous or ophthalmic tests has necessitated the development of constitutional reactions in order to arrive at a diagnosis. There is no doubt that there may be a strict localization of the hypersensitiveness in certain anatomical structures such as the intestinal tract or the bronchi. This seems to apply particularly to that group of cases in which the hypersensitiveness is to drugs and foods.

This test has to be carried out with extreme caution on account of the severity of the symptoms that may ensue following the application of the test either by subcutaneous injection or by ingestion.

In those cases in which the drug or food has been ingested, an interval of from fifteen to twenty minutes elapses before the reaction begins. Following subcutaneous injection the reaction is almost immediate on account of the more rapid absorption. Reference has been made under Cutaneous Reaction to cases which illustrate the constitutional manifestation with negative cutaneous reaction both to drugs and to foods.

As in the cutaneous and ophthalmic tests, the constitutional reactions vary in their intensity, depending upon the quantity of allergen used and the degree of hypersensitiveness of the individual. It is the cases of what might be termed a low grade hypersensitiveness that offer the greatest difficulty, on account of the fact that the onset of symptoms is not so definite, sharp and profound, and that the symptoms may continue for a longer period of time than one would naturally expect. For example, in one case of hypersensitiveness to aspirin, the reaction continued for three weeks following the ingestion of 10 grains of the drug. Such cases demand long and careful study before one can arrive at a diagnosis that is verified by a repetition of the test and by the disappearance of the symptoms following a régime based solely upon the diagnosis.

Diagnosis.—*The History of the Patient.*—There is no question that a history of allergic conditions, such as asthma, hay-fever, eczema, and food-poisoning in the antecedents is of definite value. A careful history of the patient with regard to the attacks themselves should always be elicited. Important facts to be obtained in the previous history are the presence or absence of eczema in childhood, the conditions under which the early asthmatic attacks developed, that is, whether or not they followed simple bronchitis or pertussis, whether or not there is any seasonal variation in the attacks, whether or not they apparently develop after the ingestion of food, or of certain drugs such as aspirin or quinin, and whether exposure to animals apparently bears any relation to the attack.

In any history, great care should be taken to determine the type and character of the first few attacks as throwing the greatest light upon the underlying cause. This is important from the fact, as discussed more fully under Pathology, that the early attacks are undoubtedly due to the true underlying cause, although the later attacks may be induced by non-specific factors, such as cold, over-exertion, or overeating, which are operative only in those cases in which the bronchial mucous membrane and smooth muscle-fibers of the bronchi have become irritable.

Physical Examination.—Careful physical examinations are necessary in order to make a proper diagnosis and to differentiate those conditions enumerated under Differential Diagnosis. The examination of the sputum and of the blood for an eosinophilia is also of help.

Special Examinations.—It is, however, upon the special examinations by ophthalmic, intracutaneous, or constitutional reactions that the greatest reliance must be placed. On account of the fact that in many cases the history is inconclusive, routine testing should be done with the more important pollens, animal emanations, sachets, foods and drugs. These constitute in all about ninety tests. Cases in which these special tests have elicited no positive results must be studied in order to discover, if possible, any focus of bacterial infection. This requires careful examination of the paranasal sinuses, tonsils, and teeth. Evidence of chronic appendicitis or cholecystitis must be sought as well as infection of the genito-urinary tract and rectum. Of these foci of infection those of the paranasal sinuses, usually in association with a chronic bronchitis, are by far the most important. It is a fact, however, that the more carefully cases of bronchial asthma are studied, and the wider our range of tests and observation becomes, the fewer are the number of cases that are found to be basically infectious in origin. This is distinctly shown by the fact that up to three years ago more than 50 per cent. of the cases were ascribed to infections, whereas in the present series 85 per cent. are demonstrably allergic to, and are clinically caused by, substances other than bacterial proteins. In other words, in bronchial asthma the foci of infection that are present, while important and demanding therapeutic attention, are to be considered as complicating, and not as etiological factors.

In regard to diagnosis in general, it is essential, as far as prognosis and treatment are concerned, to beware of interpreting a positive cutaneous reaction as definitely etiological. The postulates for allergy must be fulfilled.

Differential Diagnosis.—As shown under the etiological classification, there are a number of conditions in which bronchial asthma may be simulated.

Pulmonary Tuberculosis.—This is particularly important on account of the treatment. Prognosis and differentiation depend upon a careful physical examination, examination of the sputum for tubercle bacilli, and a roentgenographic examination of the lung.

Cardiorenal Disease.—This can be differentiated by proper analysis of the urine, chemical examination of the blood, measurements of blood-pressure and examination of the heart.

Mediastinal Glands.—A pathological condition of the glands, or an enlarged thymus, from whatever cause it may be, can be differentiated by pulmonary roentgenogram and routine and special examination of the blood and urine.

Complications.—EMPHYSEMA.—This is a most common complication of bronchial asthma. It is, in a sense, a part of the asthmatic condition, and is seen in practically all these cases at the time and shortly after the attack. In those cases in which bronchial asthma has become chronic it is nearly always present and may be considered as much a sequela as a complication of the disease.

CHRONIC BRONCHITIS.—This must be considered from two points of view: (1) It is present in those cases in which no allergic factor has been demonstrated and where, therefore, it may be the essential etiological factor; (2) it is also present in those cases of long-standing paroxysmal asthma proven to be allergic in character, in which case it is a true complication. In those cases of bronchial asthma with demonstrated hypersensitiveness in which the attacks are of long standing, or have become chronic, a bronchial infection develops secondarily in at least 75 per cent. of the cases. This is significant on account of its importance in the therapeutic management of these cases. In some, the bronchial infection will disappear spontaneously on removal of the allergic factor, or upon treatment by injection with the substance to which the individual is bronchially allergic. In other cases, however, in which this bronchial infection has become deep seated, or the inflammatory reaction has become chronic, treatment must be directed against this infection as well as against the allergic factor itself. These points will be discussed more fully under Treatment.

ECZEMA.—A history of infantile eczema is extremely common in those cases which develop asthma before puberty. It is not uncommon in connection with asthma at any time and occurs in approximately 10 per cent. of the cases, although usually in a very mild form. In so far as can be shown it is more truly a complication of the allergic state, of which bronchial asthma is but one manifestation. In other words, it is not due to the one specific chemical substance producing the bronchial spasm, but is an evidence of the multiple sensitizations that occur in these individuals.

URTICARIA AND ANGIONEUROTIC EDEMA.—These bear the same relation to bronchial asthma that eczema does. In some cases in which food protein or some drug has been the cause of the bronchial asthma these conditions are manifestations of the same allergy; but this does not necessarily follow, and, although the asthma is caused by some ingested substance, the two clinical conditions are merely the manifestations of a multiple and not etiologically related hypersensitiveness. In those cases in which the bronchial asthma is caused by some substance introduced into the system by inhalation, the skin manifestations, if present, are due to some other substance.

Clinical Varieties.—ACUTE ASTHMA.—(1) Many of the cases of asthma are strictly paroxysmal in type, and when they are allergic in character the period of duration depends upon the exposure to the specific allergen. As soon as the exposure to this substance ceases, the attack subsides and in the course of a few days the individual is as well as a normal person and remains so until the following exposure.

(2) There is a type of paroxysmal asthma in which the asthmatic manifestation continues for a longer or shorter period of time, perhaps for two or three weeks, after the exposure to the allergenic substance ceases. These are usually the cases in which secondary bronchial infections have occurred and in which the bronchospasm is kept up by the local inflammatory condition of the bronchial tubes.

(3) There is a form of paroxysmal asthma in which the exposure to the allergenic substance always produces a definite attack, but in which apparently typical attacks of asthma occur not from the exposure to the allergen itself but from the inhalation of irritating vapors, exposure to severe cold, over-ingestion of food, etc. These cases are somewhat confusing, on account of the occurrence of irregular, nonspecific attacks of bronchospasm. The explanation for these attacks is more fully set forth in the section treating of Functional Pathology.

CHRONIC ASTHMA.—This may be subdivided into two varieties, in both of which dyspnea is a more or less constant manifestation, although exacerbations occur from time to time. In one variety the chronic asthmatic condition is continuous on account of the fact that there is persistent exposure to the exciting cause. In practically all of these cases, however, a secondary bronchial infection exists. The other variety of chronic asthma which we see is that in which the chronic bronchitis with an associated emphysema is the essential cause of the condition, and allergic factors are apparently absent.

MULTIPLE SENSITIZATIONS.—It must be borne in mind that over 50 per cent. of the cases of bronchial asthma show a hypersensitiveness to more than one allergen. In other words, an individual may have bronchial asthma from pollens, animal emanations and foods, and in addition he may be the victim of acute or chronic bronchial infection. In such cases reflex bronchospasm is apt to occur, so that the picture is frequently an extremely puzzling one unless all of these factors can be properly demonstrated by cutaneous or constitutional reactions.

Types.—The etiological types of asthma can now be discussed with reference to the above-mentioned varieties.

(1) POLLEN ASTHMA.—There are here two well-defined groups: (*a*) the spring type, and (*b*) the fall type.

(*a*) The *spring type* of pollen asthma, corresponding to that of hay-fever, is due to the pollens of grasses, occasionally to those of trees, shrubs and flowers. Practically all of these cases suffer at the same time from hay-fever symptoms, which are followed in about two weeks by manifestations of the asthma. These cases are strictly seasonal, appearing from the middle of May to the middle of July. In a certain number the asthma does not stop with the disappearance of the pollen but continues for perhaps from two to four weeks. In practically all these cases the continuance of the asthma is due to a secondary bronchial infection.

(*b*) The *fall type* of pollen asthma is also associated in practically all cases with hay-fever, the season for which lasts from the middle of August to October or until frost appears. Here again the asthmatic manifestation does not begin as soon as the hay-fever although, if the season is abrupt and the exposure has been severe, it may begin at once. The allergen in these cases is the pollen of ragweed, or of goldenrod, aster, or any of the late fall flowers. In practically all cases, however, the ragweed pollen is the most important factor. This fall variety of asthma is, as a rule, more intense than the spring type. In many cases the asthma disappears with the frost, but in a considerable number of cases the manifestations continue for a month or perhaps two months, and in these cases the secondary bronchial infection is the real factor in the prolongation of the attack.

(2) ASTHMA FROM SACHETS AND PERFUMES.—Individuals in whom the inhalation of sachets and perfumes induces an asthmatic attack manifest these attacks as acute or chronic from the start, depending upon the frequency of exposure. If, for example, they happen themselves to use that form of sachet or perfume that produces the attack, it is continuous from the start. If, on the contrary, they are sensitized to some form to which they are rarely exposed, the attack is strictly paroxysmal and depends entirely upon their exposure. In these cases also the attack of bronchial asthma is often associated with the manifestations of a so-called hay-fever, but differs from what we know clinically as hay-fever by the fact that there is no seasonal variation whatsoever in their history.

(3) ANIMAL ASTHMA.—This is always due to the absorption of the fine epithelial scales emanating from animals, and is also usually associated with the preliminary evidence of an acute coryza. Many examples are now on record of asthma caused by the emanations from horse, cat, dog, cow, bird, rabbit, guinea pig, chicken and goose. The importance of the last two is due to the fact that the feathers when used in pillows may give rise to attacks in hypersensitive individuals. Cases allergic to any of these emanations manifest their asthma in the acute, subacute, or chronic form, depending upon the exposure and depending also upon the presence or absence of secondary bronchial infections.

(4) FOOD ASTHMA.—There are cases so exquisitely allergic to some food substance that the attack manifests itself when the antigenic substance has barely passed the mouth. At first there is a tingling, numbness and swelling of the tongue, pharynx and fauces, a sense of fullness of the head, and swelling of the nasal mucous membrane; the dyspnea that immediately follows is apparently due in some cases not so much to true bronchospasm as to edema of the glottis. When the food has been swallowed, acute abdominal pain may develop, and usually there is a marked colliquative diarrhea. In the course of a very few minutes there are manifestations of a general hyperemia of the skin with urticaria and even angioneurotic edema. The food proteins which usually give rise to these reactions are either egg, wheat, milk, fish or shellfish. These cases may be very severe, and in a few exceptional in-

stances death has ensued. As a rule the symptoms develop so suddenly that the individual does not have time to swallow a sufficient amount of the protein to bring about a fatal reaction.

More commonly the manifestations of food allergy are less acute. They give a definite history of gastro-intestinal disturbance, either the mild symptoms of indigestion with pyrosis and eructations of gas, or more striking symptoms, which resemble those of peptic ulcer, chronic appendicitis or chronic cholecystitis. In these cases the asthma is associated with the gastro-intestinal disturbance. On the other hand, the intestinal symptoms may be entirely absent, the only manifestation of allergy being the production of an attack of bronchial asthma. The acuteness or the chronicity of the attack depends upon whether it happens to be produced by one of the common foods ordinarily ingested, or by an exceptional food taken at longer or shorter intervals. As a matter of fact, it can be safely said that any article of food may produce these manifestations.

(5) DRUG ASTHMA.—The acute cases are exactly similar to the acute cases of food-poisoning and develop all of the symptoms mentioned above as associated with that condition except the cutaneous, which are more apt to be absent than present. This is the commonest type which has thus far been clinically demonstrated and proven, and the cases have been due to the ingestion of either quinin or arsenic or of one of the salicylic compounds, especially aspirin. It has been proven, however, that a drug, if habitually used, can be a factor in the production of less acute manifestations or even of a chronic asthma.

(6) ASTHMA AND BRONCHIAL INFECTION.—That the bacterial proteins themselves act in an allergic capacity has not yet been proven except in a very few of the many cases in which bronchial infections occur. We can distinguish two types of bronchial asthma in connection with infections, namely the acute and the chronic.

In the acute variety the attacks are sudden, sharp and paroxysmal in character and associated with a bronchitis, there being no other allergic factor demonstrable. Mention has already been made of the bronchial infections, which are plainly secondary to asthmatic attacks of a strictly allergic type. Chronic bronchial infections may also be seen as apparently primary etiological causes in the production of a chronic asthma. They are, for the time being, considered primary because there is no demonstrable allergic factor. Such types are not infrequently associated with chronic suppurative infections in the tonsils or paranasal sinuses. In chronic bronchial asthma that is demonstrably allergic we see a secondary bronchial infection in a large percentage of cases.

Any and all types of organisms are cultured from these cases of bronchial infection, whether acute, chronic, primary or secondary. *Streptococcus viridans,* pneumococcus, *Streptococcus hemolyticus,* influenza bacillus and *Staphylococcus aureus* are most often found. More rarely *Streptococcus mucosus* or *Pneumococcus mucosus, Micrococcus catarrhalis* and diphtheroid organisms are recovered.

(7) BRONCHIAL ASTHMA FROM DISTANT FOCI OF INFECTION.—In a few instances bronchial asthma has apparently been caused by an infection not in any way related to the respiratory tract. For example, among 250 cases studied, there was one in which it was apparently due to a chronic infection of the gall-bladder, and another in which it seemed to depend upon a chronic appendicitis. That these infections acted in a strictly allergic form was not proven in a manner to fully satisfy the postulates for allergy previously laid down, but the condition of chronic asthma abated immediately following operation. Up to the end of a year and a half the symptoms have not shown any tendency to return.

(8) REFLEX ASTHMA, OR BRONCHOSPASM.—This is a special variety which must be understood in order that one may understand asthma. It is induced by a heterogeneous group of causes such as over-exertion, over-eating, inhalation of dust and irritating vapors, or exposure to intense cold and dampness. In other cases it seems to be induced reflexly from some cause such as chronic infection of the intestinal tract, especially of the gall-bladder and the appendix, or disorders of the pelvic organs; in women it is associated with menstruation. The importance of appreciating this group of cases lies in the fact that the attacks occur only in those who have acquired the asthmatic habit from previous attacks due to true allergic influences.

Treatment.—SYMPTOMATIC TREATMENT.—In the midst of an acute attack it is not always possible to determine and treat specific causes. In such cases procedures for temporary relief are indicated.

Medicinal Treatment.—All drugs, and especially **aspirin,** should be used sparingly, as allergic reactions may result from their use.

Epinephrin 1/1000, minims 5-15 (0.3-0.92 c.c.), given hypodermically, will bring almost instant relief. In some cases even 1-3 minims (0.06-0.18 c.c.), diluted with saline, will accomplish as much. A few individuals react badly to this drug, and in these cases it cannot be used.

Morphin sulphate is essential in very severe attacks. By mouth the dose is 1/6 to 1/4 grain (10 to 16 mgm.) and by hypodermics 1/8 to 1/4 grain (8 to 16 mgm.), repeated as indicated.

Atropin sulphate, 1/100 to 1/200 grain (0.06 to 0.03 mgm.), and **nitroglycerin,** 1/100 to 1/50 grain (0.06 to 0.13 mgm.), help in some cases.

Antipyrin, 5-10 grains (0.324-0.650 gram), well-diluted, should be tried.

Benzyl-benzoate, a new preparation, has been well recommended, in doses of 20 to 30 minims (1.25 to 1.90 c.c.) every four hours. However, it has not proven itself of any great value in the experience of the author and, in one case, produced a marked general urticaria after the second dose.

Syrup of ipecac to induce vomiting in children often aborts a paroxysm.

Inhalants.—Various asthmatic powders and cigarettes on the market serve as valuable aids in affording temporary relief. A few whiffs of

chloroform may be tried in severe cases but care should be taken not to establish a habit.

General Measures.—Free **catharsis** and limitation of **diet** give relief in many severe cases. Without regard to the food allergens, which will be discussed later, a general restriction of food serves to lessen those reflex paroxysms so common in long-standing cases with a well-established asthmatic habit.

In the opinion of the author, **climate** plays no essential rôle in bronchial asthma, except in so far as it tends to improve an associated complicating bronchial infection. Only excessive cold acts in a non-specific way to produce attacks in those in whom the habit is established. The only benefit supposedly due to change of climate is in the removal of the patient from the allergenic substance in his usual environment. Often quite as complete relief is afforded by a change across the street as by a sojourn in some distant clime.

Specific Treatment.—In all cases accurate diagnosis of the specific cause is the only basis upon which proper advice and treatment can rest. It must be borne in mind that the hypersensitive individual in most cases is *allergic* for life, and that so far as is known to-day no treatment can permanently remove this hypersensitiveness. The management of the cases can be best considered according to the specific etiological factors:

(1) *Pollen Asthma.*—Those cases reacting to the pollens of grasses find it impossible to avoid the attack by removal to any climate. Those reacting to the pollens of ragweed can avoid the trouble in the White Mountains, in parts of the Adirondacks, in the Maine woods, at Mackinac Island, in Southern California and Florida, and anywhere outside of North America. For those who cannot avail themselves of travel, treatment by specific therapy in the form of **injections of their specific allergens** is definitely indicated.

Spring and fall types, due to pollens of grasses or ragweed respectively or to whatever other pollens are indicated by the tests, should be treated by injections with the specific antigen. Prophylactic therapy is best. Here the injections are begun from four to six weeks before the anticipated attack and are given in gradually increasing doses at about weekly intervals and continued through the season. In this way from 12 to 15 injections are given. Preparations of these extracts can be obtained on the market, having been accepted by the Council on Pharmacy of the American Medical Association and placed on the list of new and non-official remedies for 1919.

Phylactic treatment can also be used in cases in which the attack has already developed. In such cases, minute doses can be given at first every day, then every other day, gradually increasing the dose and the interval. In many such instances remarkable relief is afforded.

Treatment, whether phylactic or prophylactic, must be based upon the degree of hypersensitiveness, as indicated by the reactions to dilutions of the allergen, using solutions standardized according to their nitrogen content. We may say in general that those cases which show marked reactions to a solution of 0.005 mg. nitrogen per c.c. require an initial dose of 0.0001 mg. nitrogen and a maximum dose of 0.01 mg., whereas those showing marked reaction to a 0.05 solution receive an initial dose of 0.001 and a maximum dose of 0.1 mg.

Results.—The end results of cases, whether treated phylactically or prophylactically, are practically the same if we consider the effects obtained one week after phylactic treatment is begun. Of 135 cases of pollen asthma treated phylactically and prophylactically, all showed associated symptoms of hay-fever. The comparative results on asthma and hay-fever in these cases are tabulated as follows:

Asthma not improved	5 per cent.
Asthma slightly improved	6 per cent.
Asthma greatly improved	36 per cent.
Asthma absent	53 per cent.
Hay-fever not improved	4 per cent.
Hay-fever slightly improved	5 per cent.
Hay-fever greatly improved	85 per cent.
Hay-fever absent	6 per cent.

In other words, 89 per cent. gave satisfactory results. It is a curious fact that the asthma is more readily controlled than the hay-fever, as 53 per cent. showed no signs of asthma, while only 6 per cent. were entirely free from hay-fever. It will be observed that the word "cure" is not used, nor should it be, as the effect of the injections is temporary and treatment must be repeated each season.

A word of caution must be introduced here with reference to these injections, particularly in the cases of pollen sensitization with an asthmatic manifestation, as an asthmatic attack may be precipitated in those exquisitely sensitive by a dose that is clinically innocuous in those less sensitive. These attacks may be dangerous where they occur within half an hour of the injection, and they should be promptly recognized and counteracted by the injection of **epinephrin.**

(2) *Asthma from Perfumes and Sachets.*—These substances should be removed from the environment. Treatment by injections can accomplish as much as in pollen asthma, but as the effect is transient there is rarely an indication for such therapy.

(3) *Asthma from Drugs.*—The diagnosis is sufficient and avoidance should be religiously pursued. No other treatment is indicated.

(4) *Asthma from Foods.*—No treatment is indicated save in those cases, usually occurring in children, where the sensitization is multiple and includes all such important articles of diet as milk, egg and wheat. These cases are fortunately rare, but as nutrition would be seriously interfered with by their absolute exclusion and as this elimination is practically impossible, treatment by injection should be carried out. In these cases very satisfactory results ensue.

(5) *Asthma from Bacterial Proteins.*—In these cases the usual vaccine is preferable to the solution of bacterial protein. If a focus containing the bacteria can be found, it should be eliminated. It is ad-

visable to continue injections for a long time, two to three months, giving from three to six billions as a maximum dose.

(6) *Asthma Due to or Complicated by Chronic Bronchial Infection.*—Autogenous vaccines yield results, although some cases are curiously resistant; treatment should be continued for several months after the organism has disappeared from the sputum.

Prognosis.—In general it may be said that the earlier the diagnosis is made the better is the prognosis, in view of the fact that emphysema, cardiac hypertrophy, and chronic bronchial infections are less likely to have occurred and that the asthmatic habit is not so firmly established. On the other hand, many cases of long standing, from seven to twenty-five years, have been completely relieved.

The specific cause or causes are determinable in 85 per cent. of all cases as due to some allergen not bacterial in origin; this allergen is an extrinsic and removable cause in 35 per cent. of these cases, and is susceptible to treatment by specific therapy in the balance with favorable results in approximately 90 per cent. In view of this fact it may be said that the only drawback to a good prognosis is the fact that all specific therapy is to-day only temporary in its effects. The duration of the clinical immunity depends entirely upon the degree obtained by the injections; the longer they are continued and the larger the doses, the longer is the period of freedom.

Bronchial asthma in children, the result of a hypersensitiveness to food, is very apt to undergo a spontaneous cure, whereas that due to pollens, animal dust, sachets and drugs is in practically all cases so far observed a permanent reaction.

Pathology.—ORGANIC.—The organic changes found are the result of repeated or long-continued paroxysms.

Lungs.—Emphysema is practically always present. In a few instances where the paroxysm has been so violent that death seemed imminent from asphyxia, and artificial respiration was resorted to, a rupture of the lung with mediastinal emphysema extending to neck and trunk has been observed.

Bronchi.—The bronchi are often thickened and the mucous membrane is edematous, especially when the secondary infection has been of long standing.

Chest.—In children pigeon-breast results after a very few attacks. This condition is permanent even though the asthma undergoes spontaneous cure.

Heart.—Hypertrophy, especially of the right ventricle, ensues as the result of emphysema of any considerable degree.

FUNCTIONAL.—The hypersensitiveness of the smooth muscle-cells and mucous membrane of the bronchial tree to some allergen or allergens is the characteristic and outstanding feature of all functional changes in the asthmatic patient. Aside from the inheritance factor there is to-day no available explanation for this peculiar alteration from the normal in all cases of human hypersensitiveness, whether in the bronchi or in the cells of other organs of the body. One fact can be stated, however, and that is that the condition of human hypersensitiveness in any and all of its clinical forms is established spontaneously and not artificially by the usual immunological process. For further discussion of this point the reader is referred to the sections on Anaphylaxis and Allergy in the article on Hypersensitiveness. (Vol. I, Chap. vi, pp. 110 and 154).

Other functional changes frequently encountered in cases of bronchial asthma are, abnormally low blood-pressure, gastric hyperacidity and continuous hypersecretion, attacks of diarrhea with excessive mucus in the stools, vasomotor instability manifested by dermographia and hyperhidrosis. In fine, the asthmatic individuals seem to belong to that group designated as vagotonics, and this fact is further supported by the characteristic reaction to pilocarpin, and by the effect of atropin and epinephrin.

The study of bronchial asthma thus far has led the author to the belief that this vagotonic state is the result of repeated allergic reactions rather than that asthma develops in previously determined vagotonic individuals.

Another interesting point in the functional pathology of asthmatics is the establishment of the so-called "asthmatic habit." All cases of any duration give a clinical history of paroxysms of asthma due to such non-specific factors as over-exertion, over-eating and exposure to extreme cold and irritating vapors. In the history of all such cases the early attacks were definitely paroxysmal with an interim in which normal health prevailed; only after repeated attacks had been induced did the non-specific factors become operative. In other words, repeated attacks from a specific allergen eventually produce such an unstable equilibrium and an intense irritability in the cells of the bronchi that they are affected reflexly by any stimulus in the domain of the extended vagus system. Finally these reflex paths become so established and the instability so great, that any and all transitory and trivial stimuli produce great and prolonged effects, always translated in the asthmatic patient into terms of bronchial contraction and congestion. Hence the establishment of the asthmatic habit.

The conception of bronchial asthma as an allergic reaction is so recent that the whole study is in a constant state of change and progress, and it is difficult to deal as didactically as one would wish with many of its phases. With further investigation great strides should be made in discovering new etiological factors and, especially, it is to be hoped that the treatment will be so perfected that the effects of the clinical immunity now obtained may be more permanent.

BIBLIOGRAPHY

For literature which might pertain to this subject, see Bibliography on Allergic Coryza (pages 490-492).

CHAPTER III

DISEASES OF THE LUNGS

By Louis Francis Jermain, M.D.

Congestion of the lungs, p. 519—Pulmonary edema, p. 524—Hemoptysis, p. 527—Embolism, thrombosis and infarction of the lung, p. 531—Cirrhosis of the lungs, p. 534—Pneumonoconiosis, p. 541—Emphysema of the lungs, p. 544—Pulmonary abscess and gangrene, p. 554—Tumors of the lung, p. 565.

CONGESTION OF THE LUNGS

Pulmonary congestion is a hyperemic condition initiating or accompanying acute general and pulmonary infections and chronic lung and heart diseases. It is usually described as being of two types, active and passive. Passive congestion is of two varieties, hypostatic congestion, and the brown indurative form. In the light of our present knowledge all these conditions appear as symptomatic affections.

Etiology and Pathology.—Active hyperemia occurs most frequently as the initial stage of bronchial and pulmonary infections and the congestive stage of constitutional infections initiated with a chill. More rarely it develops as the result of the inhalation of extremely hot or cold air or irritating and poisonous gases. Several years ago a number of deaths occurred in this city among firemen from inhalation of the fumes engendered by the breaking of a carboy of nitric acid.

Chlorin, bromin, phosgene and other gases have been extensively employed as an offensive and defensive weapon in the recent war; they produce severe and fatal pulmonary congestion and edema. The extent of the damage depends upon the concentration and severity of exposure. In death from "gassing" the lungs are found to be intensely congested and edematous. Edema of the larynx and bronchi is found. Microscopically, the alveoli are filled with serous or fibrinous exudate, red and white blood-cells and desquamated epithelium. Numerous thrombi are seen in the smaller vessels. (Norris and Landis.)

Underhill divides the gases employed in the recent war as follows:

1. Asphyxiant or suffocating gases such as chlorin, phosgene, diphosgene and chlorpicrin.
2. Tear gases or lacrimators such as xylil and benzyl bromid.
3. Sneezing gases or sternutators, diphenylchlorarsin.
4. Blistering gases or vesicants, yperite or mustard gases.

Chlorin, phosgene and chlorpicrin destroy the epithelium lining the respiratory tract, allowing various pathogenic organisms to invade the bronchioles and lung tissue, thus producing pneumonia, necrosis, and edema of the lungs and blood concentration.

That fatal active congestion of the lung may develop from overexertion is doubtful, although such cases have been described. It is much more probable that in these cases death was due to acute left ventricular dilatation with passive congestion of the pulmonary circuit. Clinically one of the most violent examples of active pulmonary hyperemia observed by the author occurred in a patient in the initial stage of smallpox. Severe active congestions, the result of the inhalation of irritating substances, commonly terminate in edema of the lung. This is undoubtedly the result of the corrosive and destructive action of the substance upon the alveolar epithelium and capillary endothelium.

In affections of the brain, particularly the pons and medulla, active congestion may occur. The pulmonary congestion in death from an electric shock is probably of this type.

Passive congestion of the mechanical type may be:

(*a*) Acute: the result of acute left ventricular dilatation.

(*b*) Chronic: the result of mitral disease or of other conditions chronically interfering with the proper flow of blood from the pulmonary veins. The latter is generally known as the brown induration type. In this form there is distention of the alveolar capillaries, overgrowth of connective tissue, and exudation into the alveoli. The lung is dark brown in color, changing to a bright red upon exposure of the cut surface to the air, the result of the oxidation of excessive hemoglobin. Excessive hemolysis occurs in the distended vessels; and blood-pigment is deposited in the tissues and in the cells which later fill the alveoli, and appear in the sputum. Our conception of the type of cell bearing the pigment has undergone considerable modification. A large number of observers at present believe that these cells are endothelial leukocytes and not epithelial cells.

Hypostatic congestion is most commonly found postmortem. It usually represents a terminal event, the result of posture and failing circulation. It may be found shortly before death in any condition in which circulatory failure is gradual. The dependent portions of the lung are dark, engorged, heavy and upon sectioning, drip with blood and serum. The alveoli are filled with serum, blood and degenerated epithelium. It is probable that diminished aëration of the lung is an important factor in the development of hypostatic congestion. The extreme grade of this type of congestion found in morphin poisoning by Osler may be explained upon this hypothesis. Hypostatic congestion in cerebral apoplexy may possibly be of the same origin. Hypostatic congestion frequently develops in the aged following fractures of the femur, and always proves a serious complication.

Symptomatology.—Active congestion of the lungs in the large majority of instances simply represents the initial stage of some acute pulmonary or constitutional infection; hence the onset is sudden, with a chill, pleuritic pains, dyspnea, cough, and expectoration—usually of frothy and bloody material. The range and duration of the temperature varies with the nature of the infection or irritant. A tightness and fullness of the chest is usually complained of, and the active pulmonary congestion may be reflected in congestion of the skin of the face, neck and chest and the sclerotic coat of the eyes.

In extreme congestions resulting from violent irritants such as intense heat or cold, nitric acid fumes, bromin or other irritant gases, intensely agonizing and dangerous symptoms develop with great rapidity. Intense congestion of the lungs has been observed by Oliver as the result of the inhalation of carbon monoxid and sulphuretted hydrogen gases and from fumes of nickel carbonyl, and ferric carbonyl. He classes poisonous gases as: (1) "toxic, such as carbon monoxid, water gas, etc., which interfere with the oxygen-carrying power of the red corpuscle; and (2) irritant, such as nitrous and nitric acid fumes, chlorin, bromin and hydrochloric acid, which act by irritating and destroying the cell lining of the alveoli." Both these types of gases cause asphyxia. Toxic gases affect chiefly the central nervous system, producing vertigo, vomiting, headache and narcosis. Interest in poisonous, irritating gases has been especially aroused by their extensive use in the recent world conflict. In general, the symptoms produced are those of violent irritation of the respiratory tract, and these as well as the result vary with the concentration and duration of exposure. The symptoms as described by Hill are those of intense inflammation of the respiratory tract with profuse secretion of thin, watery mucus, and pulmonary edema. There is subnormal temperature, dyspnea, orthopnea, cyanosis, cough and expectoration of frothy, watery material. Later symptoms are those of severe bronchitis with fever, dyspnea, purulent expectoration, and circulatory depression. In nitrous and nitric acid inhalation, alarming symptoms may be delayed from twenty-four to forty-eight hours, when quite suddenly symptoms of acute edema and death may occur. Mandel and Gibson described the symptoms of "mustard gassing" as conjunctivitis, excessive lacrimation, laryngeal and bronchial irritation, and superficial burns. Bronchopneumonia was the most frequent complication.

Major G. B. Peat reports upon 65 cases of "gassing" received at a clearing station. All severe cases showed extreme restlessness; some were pale, others pallid, with leaden-hued mucosa and nails; cough was present in 60 per cent. The physical signs were much like those of an acute asthma. Oxygenation was bad in all but 7 cases, the lips in 12 or 13 cases being absolutely blue. There was a burning sensation in esophagus and stomach with nausea, vomiting and obstinate constipation. The chest is usually somewhat distended, and respiratory excursion is limited and accelerated. Pulmonary resonance may be impaired, and breath sounds are roughened. Crepitant, subcrepitant and dry râles may be audible. Following the inhalation of irritant gases, physical signs of edema, lobar or lobular pneumonia may be present, and physical evidence of permanent alteration of pulmonary structure remains.

The symptoms of PASSIVE CONGESTION of the brown induration type represent the manifestations of loss of pulmonary compensation in mitral or myocardial disease and consist of dyspnea upon slight exertion, orthopnea, cough with or without expectoration, respiratory acceleration and a sense of thoracic oppression. The sputum is apt to be bloody and there may be actual hemoptysis. The cough is induced and aggravated by exertion. Resonance may be impaired, thoracic movements restricted, the vesicular murmur diminished and roughened, and moist râles present. Examination of the sputum reveals blood-cells and large numbers of pigmented alveolar cells, "heart-failure cells."

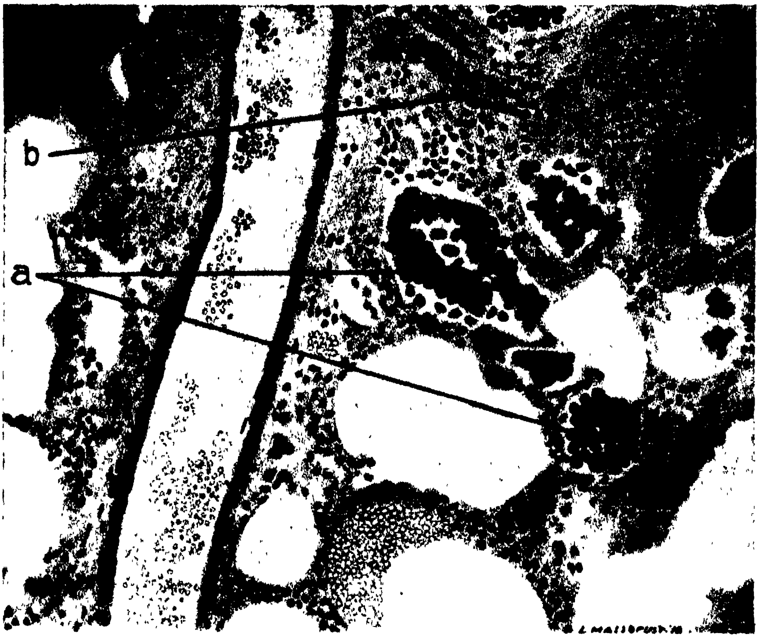

FIG. 1.—LOW POWER CAMERA LUCIDA DRAWING OF LUNG REMOVED AT AUTOPSY FROM A CASE OF MITRAL DISEASE.

(*a*) Air-cells filled with so-called heart-failure cells, (*b*) heart-failure cells in tissue near a large blood-vessel. (McJunkin.)

The symptoms of HYPOSTATIC CONGESTION are few and indefinite, and as they occur mainly in connection with prolonged infections and adynamic states they are frequently overlooked. Accelerated respiration, increased cough and dyspnea and the development of cyanosis may be the only indications of its presence. Dullness on percussion over the dependent portions of the lungs, bronchovesicular and bronchial breathing, and numerous moist râles, are found upon physical examination.

Diagnosis.—This, as a rule, presents little or no difficulty. The differential diagnosis must be based upon the history of onset, a consideration of the etiologic factors involved, and the presence of cardiac disease. The recumbent position in severe disease, complicated with marked circulatory impairment, favors hypostatic congestion.

Treatment.—The treatment of all forms of pulmonary congestion is that of the condition with which it occurs. Active *hyperemia* of the lung in acute infections, such as croupous or bronchopneumonia, bronchitis, etc., may be regarded as analogous to active hyperemias occurring in infections elsewhere in the body. This initial hyperemia possibly constitutes a protective and defensive mechanism, and the degree to which it should and can be combated is questionable. Any measure which might interfere with nature's protective processes should be avoided. The patient should be put absolutely at **rest in bed,** and small doses of **morphin** administered hypodermatically for pain and severe cough. A very light and warm **pneumonia jacket,** loosely applied, is permissible, while all heavy poultices and pastes are contra-indicated. Upon subsidence of the acute symptoms stimulating **expectorants,** such as the muriate or carbonate of ammonia, may be used. The treatment of "*gassed*" individuals as advised by Major Peat is plenty of **fresh air, oxygen inhalations** and **oxygen given subcutaneously** in the pectoral region. Absolute rest is necessary. For *severe cyanosis* **venesection** is practiced. Cardiac stimulants such as **camphor** and **caffein** are of value. **Expectorants** give relief. **Morphin** must be administered in severe cases for restlessness.

Through experiments upon dogs, Underhill determined that in the treatment of chlorin, phosgene and chlorpicrin poisoning it is of importance to maintain the blood concentration at a normal level by venesection and salt infusion. "In phosgene poisoning early bleeding and delayed infusion are advocated, while in chlorin and chlorpicrin poisoning early bleeding and early infusion are imperative."

In *passive congestion* the treatment is essentially that of the underlying condition—namely, *cardiac decompensation,* the result of mitral, myocardial or coronary disease. Absolute **rest in bed** is of the greatest importance. **Digitalis** in some form is the most reliable and effective drug. For *cough, dyspnea* and *restlessness* no better remedy than **morphin** or **codein** can be employed. In severe *pulmonary engorgement with cyanosis* the **withdrawal** of 30 to 40 ounces **of blood** from a vein is often followed by immediate relief. Free **catharsis** with attention to elimination through the skin and kidneys is important.

The *prevention of hypostatic congestion* is more important and effectual than its treatment. Patients critically ill and confined to bed should not be allowed to assume the same position for any length of time. Cardiac strength and efficiency must be carefully guarded and supported, especially in those debilitated from disease or advanced age.

Prognosis.—In ACTIVE HYPEREMIA from infections the prognosis varies with the cause and is usually favorable. In congestions from inhalation of poisonous gases and violently irritating substances the prognosis is usually grave. The prognosis of PASSIVE CONGESTION depends upon the possibility of restoring circulatory balance by rest and cardiac tonics. The condition of the heart-muscle is the important determining factor. HYPOSTATIC CONGESTION develops only in severe illness associated with profound circulatory depression. In most instances it represents a terminal complication, and the prognosis must be considered unfavorable.

PULMONARY EDEMA

Edema of the lungs is usually a sequel of congestion, active or passive, and can be distinguished from congestion only by the greater amount of exudation which occurs.

Etiology and Pathology.—Edema of the lungs may be:

1. Localized, occurring in the tissue around an area, the seat of a pneumonia, abscess, infarct or a tuberculosis.
2. Terminal, commonly known clinically as the death rattle, which develops in Bright's disease, cardiac incompetency, and cerebral affections.
3. Toxic, occurring in typhoid, pneumonia, influenza, acute nephritis, polyarthritis, etc.
4. Mechanical, occurring in chronic arterial and cardiac disease, and in chronic nephritis. Edema of the lungs may also be acute or chronic.

Babcock directs attention to edema of the lungs occurring during or after thoracentesis. Stengel has described a paroxysmal variety of edema occurring in patients with arterial, cardiac or renal disease.

The mode of development of edema of the lungs has been the subject of considerable experimental study. The view held by most authors at present is that edema is the result of a combination of mechanical and toxic factors. Mere blood stasis will not lead to edema, unless there is an increase in capillary tension, as a result of marked derangement of the relative propulsive power of the two ventricles and a capillary endothelium damaged by prolonged stasis or toxemia. Bastedo, in discussing pulmonary edema in pneumonia, gives as favoring increased production of tissue fluid: (1) increased intracapillary pressure; (2) increased permeability of the capillary wall; (3) hydremia.

As factors favoring diminished removal of tissue fluid he cites: (1) lymph-stagnation; (2) diminished capillary absorption; and (3) increased molecular concentration of tissues.

Edema of the lungs has been produced by adrenalin injections.

Auer and Gates showed that intratracheal injections of moderate doses of adrenalin in rabbits whose vagi were severed produced marked pulmonary edema in a large percentage of cases. The same dose in normal animals caused only a slight effect. Artificial respiration greatly reduces the production of edema in animals treated in the above-described manner. As adrenalin exerts a bronchoconstrictor effect, evidence is submitted to show that the aspirating action of lung alveoli under this condition apparently plays an important part in the production of adrenalin pulmonary edema. Stenosis of trachea facilitates production of adrenalin edema in unvagotomized animals. Intratracheal injections in vagotomized animals produce temporary incoördination between the ventricles so that the left beats half as fast as right, causing hyperemia of and hemorrhages from the lungs. Atropin exerts a protective action against adrenalin.

Matsvoka, in a systematic study of experimental obstructive edema of the lungs, in isolated heart lungs of dogs made with the aid of the Starling heart-lung preparation, arrived at the following conclusions:

"(1) Obstructive edema of the lungs takes place when certain limits of combined arterial pressure and venous inflow are exceeded. (2) Obstructive edema is produced with a constant, moderate arterial pressure of 80 mm. Hg, when a total heart output of not less than 92 liters per hour is maintained for over fifteen minutes; or with a constant, high arterial pressure of 160 mm. Hg, when a total heart output of not less than 38 liters per hour is maintained for over fifteen minutes. (3) The production of obstructive edema is very considerably facilitated by the occlusion of the root of the aorta, when a relatively small amount of venous inflow is sufficient to produce the lung condition. (4) Edema of the lungs usually occurs more quickly and with a smaller amount of arterial pressure and of venous inflow when the pericardium has been removed. (5) Gaseous metabolism and energy consumption of the heart are decreased in obstructive edema of the lung. (6) In all cases where the experiments with the Starling heart and lung preparation were carried out to a conclusion, there was seen increase in volume following diffuse, congestive edema, unrecognizable microscopically; atelectasis; and compensatory emphysema and splenization of the lower lobes."

The edematous lung varies in color with the amount of congestion. It is heavy, mushy and from the cut surface frothy serum runs freely. The fluid can be readily expelled by pressure and patches of consolidation thereby excluded. In some instances the lung appears gelatinous, owing to the large amount of coagulated albumin and endothelial leukocytes contained in the air-cells.

Symptomatology.—The symptoms may develop gradually, being superimposed upon symptoms of passive congestion, the result of chronic cardiac, cardiorenal or general disease; or they may develop acutely in pneumonia, acidosis, general infections, and angioneurotic edema. The dyspnea and cough usually present become much aggravated. Profuse expectoration of frothy serous or bloody fluid ensues. Moist râles of all types are heard over the lungs, especially at the bases. There is intense thoracic oppression. The patient's face assumes a leaden, ashy-gray hue. The pulse becomes rapid and feeble, and death occurs from cardiac failure or asphyxia. General and rapidly fatal edema of the lungs may develop in chronic Bright's disease, pneumonia, coronary disease, valvular disease, carcinoma, or as the result of the inhalation of poisonous irritating gases. The patient may retain consciousness to the end, fully aware of the tragedy that threatens him in being literally drowned in his own serum. Aside from a profusion of moist râles and slight dullness on percussion there are no marked physical signs. Temperature is absent unless the edema develops in association with an acute infection. The expectoration is copious, frothy and serous, rich in albumin, and contains red blood-cells in abundance.

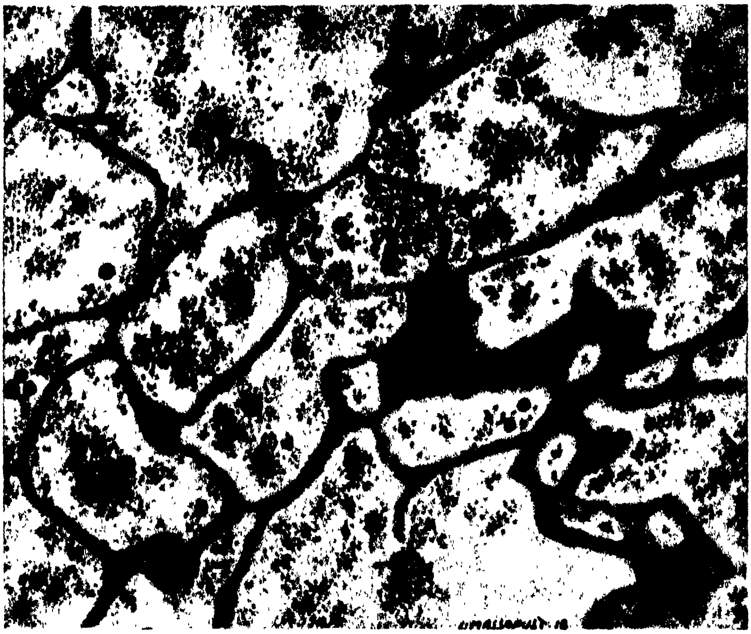

FIG. 2.—LOW POWER CAMERA LUCIDA DRAWING OF LUNG IN PULMONARY EDEMA SHOWING AIR-CELLS FILLED WITH ALBUMINOUS GRANULES. (McJunkin.)

Diagnosis.—If severe dyspnea, cough, profuse expectoration of bloody fluid, and numerous moist, bubbling and crackling râles develop during the course of any severe cardiac, renal or general disease, the diagnosis of edema of the lungs presents little difficulty. In pulmonary embolism the symptoms may resemble much those of edema. The sputum, although bloody, is never so profuse or liquid; neither are moist râles so abundant or general. Attacks of cardiac or renal asthma can be distinguished from edema by the absence of numerous moist bubbling râles. Rapid death from edema, when a history of existing disease is lacking, may lead to diagnostic error.

Treatment.—Edema of the lungs always calls for prompt and energetic treatment. This must be directed toward the arrest of the serous transudation and the amelioration of the causative condition. Counterirritation in the form of **dry cupping** may be employed. **Atropin,** although theoretically contra-indicated, in certain cases appears useful, especially if combined with **morphin.** The author has recently had under his care a patient with coronary disease and attacks of angina pectoris. In several of the numerous attacks of angina from which the patient suffered, typical edema of the lungs developed which, in every instance, was promptly relieved by the hypodermic administration of **morphin and atropin.** In the acute paroxysmal edemas described by Stengel morphin proved almost a specific. Cardiac stimulation, either by means of **hypodermics of camphor, caffein, ether or digipuratum,** or by **strophanthin intravenously,** should be instituted immediately. **Venesection** is a reliable procedure in the acute edemas of pneumonia and other infections; it may be of service in edemas of hypertension. In the case of nephritis, acute or chronic, an increased elimination by means of **diaphoresis and catharsis** may prolong the patient's life. **Free and unrestricted respiratory action** favors pulmonary circulation and should be secured in all cases. **Artificial respiration** should be resorted to when it is evident that respiratory excursions are limited.

Prognosis.—This, although always grave, depends upon the underlying disease. An attack of edema of the lungs, even if severe, need not necessarily be fatal. The author has seen a patient with mitral stenosis pass through at least four distinct attacks of edema, and curiously enough, she died without symptoms of edema. Recurring attacks of edema of the lungs in the author's experience are most common in mitral stenosis and coronary disease with angina pectoris. Edema of the lungs complicating acute nephritis, pneumonia and other acute infections may be permanently recovered from. In acute edemas of chronic Bright's disease the prognosis is very bad.

HEMOPTYSIS

Hemoptysis (from Greek *haima* blood and *ptysis* a spitting) indicates bleeding from the lungs and bronchi.

Etiology and Pathology.—Pulmonary tuberculosis is by far the most frequent cause of hemoptysis. Of 5,856 cases of tuberculosis seen by Landis at the Phipps Institute, the occurrence of hemoptysis was acknowledged by 47.6 per cent. on their first visit (Norris and Landis). Statistical evidence seems to show that slight hemorrhages occur most frequently in the early stages of tuberculosis, while the more profuse and serious types occur in the later stages. The source of the hemorrhage has been the subject of much discussion. Early and slight bleeding may arise by diapedesis from the zone of inflammatory hyperemia around a tuberculous focus. More profuse hemorrhages are probably the result of the growth of tubercles in the walls of small bronchial or pulmonary vessels, leading to rupture of these vessels, while the severe types of hemoptysis arise through rupture or erosion of large vessels within a cavity.

Hemoptysis may be the result of laceration of the lungs from crushing injury, violent blows or falls, and penetrating wounds from without. Heart lesions, especially mitral lesions during the decompensated stage, are a frequent cause of hemorrhage from the lungs. The amount of blood lost as a rule is not large, but the bleeding, especially in the mitral stenosis, may persist for a considerable period of time and show tendency to recur upon exertion.

Ulcerative lesions of the larynx, trachea or bronchi may give rise to hemorrhage. These lesions are usually of a malignant, syphilitic, or tuberculous nature; the amount of blood lost varies greatly. Considerable blood may be expectorated during the congestive stage of pneumonia and other acute pulmonary infections. Great care should, however, always be exercised in excluding tuberculosis in such cases.

Hemoptysis from aortic aneurism eroding the trachea, bronchi or lung tissue is quite common. The hemorrhage may be small in amount, "weeping," and continue for a considerable length of time. Rupture of the aneurysmal sac with profuse and fatal hemorrhage may follow this slight bleeding or may occur without previous warning. Careful physical and *x*-ray examination of the chest will reveal unmistakable evidence of aortic aneurysm.

Abscess, gangrene, infarction and malignant disease of the lung, mycosis, distomatosis, purpura hemorrhagica, acute lymphatic leukemia, and scurvy may all give rise to pulmonary hemorrhages. So-called vicarious hemoptysis, hysterical pulmonary hemorrhage, the hemorrhage of adolescence and hemoptysis following heavy lifting, will upon careful investigation by means of modern physical and roentgenographic methods in the majority of instances be proven to be due to tuberculous disease.

Symptomatology and Diagnosis.—Hemorrhage from the lungs is usually sudden and associated with cough. It may be small in amount, simply streaking the sputum, giving it slight color; or it may be profuse and rapidly fatal. A sensation of warmth in the throat and a salty or sweetish taste usually heralds the appearance of the blood. Blood from the lungs is frothy, alkaline, and mixed with sputum, and is thus distinguished from blood from the stomach. It must be remembered, however, that considerable quantities of blood may be swallowed and later vomited. A patient's version as to the alimentary or respiratory origin of blood is not always reliable. Hemorrhage in pulmonary tuberculosis may vary in amount from a simple tinge in the sputum to a quantity which rapidly terminates life. A tuberculous patient may die during his first attack of hemoptysis. No event in the life of an individual gives rise to more genuine fear and anxiety. Hemorrhage from aneurysm, like hemorrhage from tuberculosis, may vary greatly in quantity and duration. Bronchial, bronchiectatic and congestive hemorrhages are commonly mild and evanescent. The physical signs in hemoptysis vary with the cause. Prolonged physical examinations, particularly percussion, should be avoided during active hemorrhage. Subsequent to the hemorrhage, however, the most careful physical and *x*-ray examinations must be insisted upon. A stereoscopic roentgenogram will frequently reveal a lesion which it is impossible to detect or outline by physical examination. Our views concerning the location and development of pulmonary tuberculosis have been radically altered through the work of Birch-Hirschfeld, Ghon, Cunningham, Miller and Dunham. Readers interested in this subject will find it exceedingly profitable to refer to the work of Miller and Dunham. The expectoration of any considerable amount of blood almost always means pulmonary tuberculosis.

Treatment.—This consists in:

1. The arrest of the hemorrhage.
2. The prevention of its recurrence by favorably influencing the causative condition. Absolute rest, both physical and mental, should be obtained as promptly as possible. The best position is probably the semi-recumbent one on a couch or bed. The patient's anxiety should be allayed by positive assurance that the amount of blood lost is trivial, that death from hemorrhage is rare, and that the bleeding will soon cease. If the hemorrhage is at all profuse a hypodermic of **morphin and atropin** should be administered at once. It is best to keep the patient slightly under the influence of these drugs as long as the hemorrhage persists. **Cold** applied to the chest, in the form of **cloths** wrung out in ice water, or the **ice bag,** is frequently recommended, but is of doubtful value unless applied directly over the heart. The **hot-water bag** applied over the dorsal spine has been recommended by B. O. Kinnear, who claims that it produces arterial contraction to a marked degree. *Ergot,* probably the most frequently employed drug in the control of hemorrhage, is not only useless, but may be positively harmful. *Styptic and astringent remedies* can be of little value. **Atropin, nitroglycerin, aconite,** and **veratrum viride** have been recommended, and may be administered with advantage in some cases. The prompt **inhalation of amyl nitrite** is of unquestionable value. **Coagulose** is at present widely used for the control of hemorrhage from all parts of the body. It is the trade name for a powder obtained by precipitating normal blood-serum, and is used locally, or by subcutaneous injection, for the purpose of increasing the coagulability of the blood. Its value, however, in pulmonary hemorrhage is doubtful. Blood-coagulants, as normal serum, diphtheria antitoxin, or blood transfusion, as well as hemoplastin and similar preparations may be used. Emetin hydro-

chlorid may also be of service.* **Gelatin** and the **calcium salts** are recommended by some for similar reasons. There is some danger connected with the subcutaneous use of the former, while the effect of the latter is uncertain and transient. *Cough should under all circumstances be controlled by the use of* **morphin** until such time as firm closure of the eroded vessel has taken place. Codein may after a few days be substituted for the morphin. In all cases the bowels should be kept freely open by means of mild laxatives. *In a large majority of patients pulmonary hemorrhage means pulmonary tuberculosis;* hence, the rational and persistent treatment of the tuberculosis is most successful in the prevention of recurrent hemoptysis. In the early and suitable late cases of tuberculosis, the production of **artificial pneumothorax** is a most valuable procedure, not only in arresting a continuous slow hemorrhage, but also in avoiding its repetition.

Hemoptysis, the result of passive hyperemia of the lungs from mitral or other cardiac disease, is seldom severe or dangerous. Our attention, therefore, need be directed only to the underlying causative condition.

Hemorrhage from an aortic aneurysm, if not immediately fatal, should be treated like hemoptysis from any other cause. Vigorous and intensive **antisyphilitic treatment** should be instituted at once, as there is no question at present that actual rupture may at least be delayed by such treatment.

Prognosis.—Hemorrhage *per se* is rarely fatal in pulmonary tuberculosis. In advanced disease of this type, however, death may come directly as the result of loss of blood. The gravity of the prognosis arises, not from the bleeding, but from the tuberculous infection which causes it—a fact not sufficiently appreciated by medical men or patients. Early bleeding in tuberculosis, on the other hand, may be of splendid prognostic import. No other symptom will so surely bring a patient to a realization of his condition, and create in him an earnest desire to seek medical advice and follow it. The frequent desire on the part of physicians—seconded by the patient—to insist that blood expectorated does not proceed from the lungs is productive of much harm. On the other hand, to consign a patient suffering from mitral disease to a high altitude because there has been hemoptysis is equally reprehensible. Hemoptysis in active and passive pulmonary hyperemias is rarely severe. Mackenzie reports severe hemorrhage in mitral stenosis. In mitral disease it may actually give the patient temporary relief. In nontuberculous abscess and gangrene of the lung hemorrhage is rarely alarming. Mild hemorrhage "weeping" from an aneurysm of the aorta may persist for a considerable time without actual rupture occurring. When rupture does occur into the trachea or a bronchus, death is as a rule almost instantaneous.

In profuse pulmonary hemorrhages death may result not from the loss of blood, but from exhaustion, aspiration pneumonia, or actual suffocation.

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* Burdick. International Clinics, 1915, ii, 39.

EMBOLISM, THROMBOSIS, AND INFARCTION OF THE LUNG

Etiology.—Embolism of the pulmonary arteries is of rather frequent occurrence. This is not surprising, when one considers the frequency with which venous thrombosis is found, especially in the veins of the lower extremities—the pelvic and hemorrhoidal veins—and the common occurrence of venous thrombosis in the zone of infiltration in pelvic and abdominal infections.

Emboli most often have their origin in the thrombosed veins of the uterus following parturition, the femoral vein, the prostatic, pelvic, and hemorrhoidal veins. Venous thrombosis is common in typhoid fever and pulmonary embolus may result. Pulmonary emboli are not uncommon following appendicitis, particularly when the infected organ is located postcecal and high up in the abdomen.

In acute or chronic endocarditis, particularly in the ulcerative or malignant type, emboli composed of detached vegetations are common. In decompensated lesions, particularly high grade mitral stenosis leading to blood stasis in the right heart, blood coagula may form in the trabecular recesses of the right ventricle and in the auricle, and constitute pulmonary emboli. Embolism or thrombosis frequently occurs in pleurisy with effusion. The embolus, as a rule, is large, most commonly obstructs the pulmonary artery or one of its main branches, and is a frequent cause of sudden death. Tumor metastases are common sources of emboli and infarction. Fat emboli may occur, following fractures or crushing injuries to bones.

Symptomatology.—The symptoms depend upon the size of the pulmonary vessel which is occluded. If the embolus is of a size sufficient to obstruct the pulmonary artery, death occurs almost instantly with symptoms of intense dyspnea and suffocation. Most commonly the patient is one recently confined, or one who has undergone some abdominal operation, and who on the first attempt at assuming the erect posture is suddenly seized with agonizing dyspnea, clutches vehemently at his throat, becomes rapidly cyanotic and dies.

If the vessel occluded is one of the larger branches of the pulmonary artery, death may not occur for several hours, during which time the patient suffers intensely with dyspnea, anxiety and a fear of impending death. The respiration is greatly accelerated, and the heart's action is feeble and rapid. The skin becomes livid, of an ashen hue, and covered with cold perspiration. The veins are greatly distended and death may be preceded by convulsions.

The immediate cause of death is said to be cardiac paralysis: the result of sudden stoppage of coronary and general circulation, cerebral anemia, or acute dilatation of the right ventricle.

Obstruction of small pulmonary vessels leads to infarction. There is often a chill accompanied with pleuritic pain, cough and hemoptysis. The amount of blood expectorated is not large, although the sputum may appear to consist wholly of blood. Bloody sputum may persist for weeks, especially when there is repeated infarction. Even when there is no subsequent evidence of infection, a temperature rise may be observed. Infected emboli frequently result in abscess, more rarely in gangrene of the lung. Infection may occur after infarction from existing bronchitis or bronchiectasis.

The temperature in infected infarcts is septic in type; the hemorrhagic sputum may change to a purulent one containing hematoidin crystals and elastic tissue.

In the rapidly fatal cases, physical signs are usually absent or the desperate condition of the patient precludes their elicitation. Where death does not occur for several hours the breath sounds disappear over the infarcted area, crepitant, subcrepitant, and bubbling râles appear, and marked impairment of resonance develops.

Examination of the heart reveals increased area of cardiac dulness, especially to the right, marked impairment of heart sounds and frequently a systolic murmur over the pulmonary area.

Fig. 3.—Gross Drawing of Hemorrhagic Infarct in Lung. Chronic passive congestion. (McJunkin.)

Diagnosis.—This depends almost entirely upon the history of previous disease and the symptoms present. Sudden death in a patient who has pursued an uneventful postoperative, or postpuerperal course of some days' duration, is almost with certainty attributable to a large embolus of the pulmonary artery.

The absence of a history of attacks of angina pectoris and of physical signs of other cardiac disease will serve to exclude other causes of sudden death. Where life is prolonged for some hours the diagnosis is more certain. The agonizing dyspnea, cyanosis, cardiac depression and collapse, developing so rapidly in a patient previously comfortable, coupled with physical findings of pulmonary atelectasis, removes any doubt as to diagnosis.

In pulmonary infarction there is sudden pleuritic pain, a chill, accelerated respiration, cough, bloody sputum, and cardiac depression. Pneumonia can be excluded by the absence of high fever. In the presence of acute endocarditis symptoms of acute pleurisy nearly always mean infarction. Similarly the sudden development of such symptoms following operative procedures or disease conditions complicated by phlebitis leaves little question as to diagnosis.

Symptoms of pulmonary infarction following fractures and crushing injury to bone may be ascribed to fat emboli.

Treatment.—This is prophylactic and supportive. Patients suffering from conditions in which venous thrombosis or phlebitis may be suspected or demonstrated should be kept absolutely at rest until such time as organization of the thrombus may have been accomplished. In the case of phlebitis or thrombosis of the veins of a **limb** this member should be **immobilized.** Patients suffering from acute endocarditis with or without petechiæ should be kept at **rest,** preferably in bed. Where pulmonary infarction has occurred, complete rest is essential to avoid recurrence. Unfortunately sudden death from embolus of the pulmonary artery frequently occurs in patients in whom there is no reason whatever to suspect venous thrombosis. The writer has personal knowledge of several such deaths following simple appendectomies.

Obstructions of the pulmonary artery or one of its main branches by embolus are not likely to be influenced by any therapeutic measure which may be instituted. Where death does not occur shortly after development of symptoms, *supportive* treatment should be instituted. **Hypodermics of camphor, ether, strychnin or caffein** may be given as indicated. **Morphin** will allay the dyspnea and restlessness. **External heat and counterirritation** are useful in improving superficial circulation. Severe cyanosis and right ventricular dilatation may be relieved by **venesection.** In pulmonary infarction the management is entirely symptomatic. Pleuritic pains and cough should be relieved, and **rest** secured for the patient by the administration of **morphin. Codein or heroin** may later be substituted for the morphin. **External heat,** or a **sinapism** followed by dry heat, is effective in relieving pleuritic pain.

Prognosis.—Large emboli occluding the pulmonary artery or one of its large branches are practically always fatal. Incomplete obstruction of a large branch may be followed by reëstablishment of the circulation and recovery.

In hemorrhagic infarction the prognosis is favorable, unless the embolus is septic, or repeated infarctions, the result of ulcerative endocarditis, occur.

Pathology.—The pathologic changes, as well as the clinical manifestations, depend upon the size of the artery occluded, and whether or not the embolus carries with it septic material.

In probably the majority of instances the emboli are small, lodge in the lower lobe of the lung, and give rise to no clinical evidence of infarction. Large emboli, completely obstructing the pulmonary artery or one of its main branches, lead to such rapid death that little pathologic change appears in the lung tissue. When an artery of some caliber is plugged, an infarct involving the greater portion of a lobe may result. Infarcts occur most frequently in the right lung. They are wedge-shaped, with the base of the wedge toward the pleural surface, usually located peripherally, where they appear as circular, slightly elevated, dark red areas. The pleural surface overlying the infarct may show evidence of fibrinous pleuritis. On section, the infarct is found to be wedge-shaped, solid and dark red in color.

Microscopically there appears diffuse infiltration of the pulmonary tissue with red blood-cells, and at the apex of the infarct the artery occluded by a blood clot. Later findings are leukocytic and fibroblastic invasion, pigmentation, disappearance of the red blood-cells with return to normal, or—what is perhaps more frequent—fibrosis, and replacement of normal lung parenchyma by scar tissue.

Infected emboli lead to inflammation, necrosis, and abscess, or gangrene of the infarcted area. Multiple abscesses of the lung may result from septic material entering the pulmonary circulation, without actual infarction having occurred. The pleura in these cases may become the seat of suppurative pleuritis.

The factors entering into and the manner of development of pulmonary infarct have given rise to much discussion. Facts experimentally established are:

1. That the obstruction of the vessel must be complete.
2. Complete plugging of a pulmonary arteriole does not necessarily result in infarction.
3. Stasis in the pulmonary veins greatly favors infarction.

The explanation most generally accepted is as follows: in complete occlusion of an artery, all active circulation ceases in the area supplied by this artery except such as may be collateral. With a normal venous circulation, this collateral circulation may be sufficient to maintain vessel integrity and infarction does not occur. If, however, there is venous stasis, the pressure in the veins equals or exceeds that of the collateral circulation leading to complete stasis of the blood, nutritional disturbances of the vessel, and extravasation of blood into pulmonary tissue.

CIRRHOSIS OF THE LUNGS

(*Chronic Interstitial Pneumonia, Sclerosis of the Lung, Fibroid Phthisis*)

Cirrhosis (from Greek *kirrhos*—tawny) of the lung is an overgrowth of fibrous tissue in the lung. It is no longer considered a disease entity but is the product of inflammation or irritation arising from many causes. The term fibroid phthisis should be applied only to cases in which the fibrosis is the result of tuberculous infection.

Etiology.—Local cirrhosis will be found in the zone of all abscesses, bronchiectases, infarcts, gummata, cysts and localized tuberculous infections of the lungs. Limited areas of fibrosis may also be the result of recurring infection of the bronchopneumonic type. Localized fibrosis develops also as the result of such chronic infections as leprosy, glanders, actinomycosis, blastomycosis, etc.

Diffuse fibrosis of the lung, following acute croupous pneumonia, has been described by many authors. This has occurred particularly in individuals whose resistance was lowered, and in whom there was evident a tendency to low grade inflammations. Why in such individuals a fibroblastic rather than a leukocytic invasion of the fibrinous exudate takes place is not quite clear. A condition of negative chemotaxis or absence of autolysis has been advanced in explanation of this unusual phenomenon. Inasmuch as this change has been described most commonly in individuals who have suffered from repeated attacks of croupous pneumonia, the belief that a modified tuberculous infection is responsible is not unwarranted.

The pleurogenous form of cirrhosis is of two types:

(1) That due to long compression of the lung by serous or purulent exudates.
(2) That due to a chronic plastic pleuritis in which the connective tissue overgrowth proceeds from the pleura inward, along the fibrinous septa separating the secondary lobules.

The latter type is probably in the large majority of instances also of tuberculous origin.

Of all the causes of fibrosis of the lung, tuberculosis is undoubtedly the most frequent. Fibrosis of the lung in tuberculosis is an expression of resistance, hence the greater the resistance, the better the environment, the more extensive the fibroid change. It is the natural process of limitation of tuberculous dissemination, and is particularly in evidence in those manifesting a decided tendency to chronicity and in cases in which sanatorium treatment has been energetically and persistently carried out.

Fibrosis of the lung is not uncommonly the result of chronic irritation from inhalation of dust (pneumonoconiosis). Workers in iron and steel, stone-cutters and coal miners are most frequently affected. It is highly probable that not only does the deposit of such foreign material in the lungs lead to connective tissue overgrowth but it also predisposes to tuberculous invasion. Chronic bronchitis, fetid and purulent bronchitis, bronchiectasis are causal factors in pulmonary cirrhosis. Chronic inflammations and infections of the bronchial mucosa, associated with severe cough, result in bronchial cavities and cirrhosis. The cirrhosis may be primary, and bronchiectatic cavities may result from traction of connective tissue on the bronchi. Chronic passive congestion of the lungs from mitral or myocardial diseases invariably leads to a certain degree of cirrhosis analogous in its distribution to that arising from the inhalation of dust-laden atmosphere.

Prolonged compression of part of the lung by tumors, aortic aneurysm, enlarged lymphatic glands, etc., leads to induration of the compressed portion. Syphilis of the lung (probably most frequently overlooked) is a prolific cause of diffuse pulmonary cirrhosis. In the new-born it occurs in the form of the "white pneumonia" of the fetus; and in the adult as gummata or a fibrosis extending outward from the hilus of the lung.

Symptomatology.—CLINICAL HISTORY.—The symptoms consist in chronic cough with or without expectoration, and gradually increasing dyspnea on exertion. The cough has commonly been present for years, primarily perhaps only in winter, later continuously, without marked impairment of general health.

The amount and character of the expectoration depend upon the condition of the bronchial tubes rather than that of the lung itself. If large bronchiectatic cavities have formed, the sputum is apt to be profuse, mucopurulent, fetid and even bloody in character. In fibrosis, the result of inhalation of particles of foreign matter (pneumonoconiosis), the sputum contains such material. When cirrhosis becomes extensive, pulmonary circulation suffers obstruction; the work of the right ventricle is greatly increased; cardiac hypertrophy and finally decompensation with symptoms of general circulatory failure result. Pyrexia, like the expectoration, depends upon the presence of infected bronchiectatic cavities. The temperature is not usually high but when present leads to gradual emaciation and chronic invalidism. The general health of the patient depends upon the cause, degree, rapidity of development of the fibrosis, the presence of infected bronchial cavities, and the degree of right ventricular competency.

PHYSICAL FINDINGS.—These vary with the type and stage of the disease, and the age of the patient. Cirrhosis developing rather early in life, the result of some chronic pleural or pulmonary irritation or infection, leads to marked changes in the configuration of the thorax. The side affected is markedly retracted and flattened. The intercostal spaces are greatly narrowed; the costosternal angle is acute; the shoulder droops; there is lateral deviation of the spine; the scapula appears winglike; and the affected side of the chest is irregularly angular instead of round. The apex-beat is displaced toward the affected side, upward in left-sided and downward in right-sided involvement. Measurement of the affected side shows marked diminution in the circumference over that of the normal, and great restriction of respiratory excursion, especially when the opposite lung shows compensatory emphysema. Litten's sign is usually present and easily demonstrable; clubbed fingers are common. In chronic fibroid tuberculosis the flattening and deformity may be bilateral, involving chiefly the clavicular, infraclavicular and scapular regions.

Pectoral fremitus is usually increased, although it may be diminished or absent, when great pleural thickening exists. Over bronchiectatic cavities there may be exaggeration. Percussion reveals impaired pulmonary resonance, dullness and even flatness, depending upon the degree of cirrhosis and the amount of pleural thickening. Particularly evident is a sense of resistance to the percussing finger, especially wherever there is much pleural involvement. Areas of compensatory emphysema, over which a hyperresonant note may be elicited, may exist in the same lung. Over large bronchiectatic cavities, a high-pitched tympanitic or amphoric sound may be obtained. Auscultatory findings range from diminished respiratory sounds in marked pleural thickening to bronchovesicular and bronchial breathing in advanced and extensive cirrhosis. Cavernous breath sounds may be present over bronchiectatic cavities, as well as moist râles of various dimensions. Vocal resonance is diminished or exaggerated under conditions which similarly influence breath sounds. Pleuritic friction sounds, at times amounting to loud, leathery creaking noises, are present.

Diagnosis.—In massive fibrosis presenting the deformity and physical findings previously discussed, there is little difficulty in diagnosis. Minor grades of sclerosis in scattered patches are not distinguishable from pulmonary infiltration of cellular origin. A clear history of antecedent disease, the occupation of the patient, the presence of chronic cough and the duration of the affection are important in differential diagnosis. Chronic pulmonary tuberculosis of the fibroid type may give rise to identical symptoms and signs. The disease, however, is practically always bilateral, and involves by preference the apical regions. Inability to find tubercle bacilli in the sputum does not exclude tuberculosis, as this organism may be absent from the expectoration for long periods of time. Fibrosis of the lung is distinguished from fibroid tuberculosis, mainly by the absence of constitutional symptoms.

In chronic pleuritis with great thickening of this membrane and in chronic pyothorax, considerable pulmonary cirrhosis coexists (pleurogenous variety). A differential diagnosis is of little importance.

Primary or secondary new growths in the lung may for a time simulate chronic fibrosis. In a relatively short time, however, symptoms of mediastinal pressure, lymphatic invasion and cachexia develop which enable the observer to differentiate one from the other. In new growths of the lung, the heart is usually displaced toward the sound side.

In syphilis a diffuse cirrhosis of the lung may develop; this is with difficulty differentiated from other forms. Marked deformity of the chest, however, is rare. In all cases of cirrhosis of doubtful origin, a Wassermann test should be made, even if evidence of syphilis in other parts of the body is lacking. Fluoroscopic and roentgenographic examinations are of great aid in determining conditions present. Areas of fibrosis, bronchiectatic cavities, pleural thickening, and cardiac displacement are readily determined by careful analysis of the stereoscopic roentgenogram. In advanced cirrhosis and retraction of the lung, there is marked elevation of the diaphragm on the same side, with displacement of stomach or liver in the same direction.

Treatment.—When cirrhosis of the lung has once become established to the degree recognizable by clinical examination, none other than *symptomatic* treatment will be of any value. *Preventive measures* should, therefore, engage our earnest attention. The management of all croupous or bronchopneumonias showing a tendency to incomplete or delayed resolution should be a cautious one. **Pleural effusions**, particularly purulent ones, should be **evacuated**, and the cavity well drained before permanent retraction and carnification of the compressed lung takes place. In acute or chronic disease associated with violent and persistent cough, this symptom should be combated with a view of preventing bronchial dilatation and bronchiectatic cavities. When pulmonary cirrhosis has become evident, general hygienic and protective measures are important. If possible the patient should reside in an equable **climate**, and be protected from the inhalation of air laden with dust or other irritating substances. Exposure to cold and damp and acute bronchial infections should be avoided. Bodily nutrition and resistance should be maintained as well as possible. The **cold sponge bath** or **cold shower** is of decided value in resisting the tendency to bronchial infections.

Profuse expectoration from bronchial cavities calls for **codein, heroin** or **terpin hydrate**, and the **inhalation of turpentine, creosote** or **carbolic acid** in vaporized form.

In advanced cases cardiac energy should be conserved with the greatest care. If cardiac incompetency occurs, **complete rest** and **cardiac tonics** must be employed.

Prognosis.—While cirrhosis of the lung is a gradually progressive and incurable affection, the prognosis as to duration of life is not unfavorable; even a useful and fairly comfortable existence is not incompatible with this condition. This is especially true of the pleurogenous and syphilitic types, particularly when the nature of the latter form is recognized early, and intensive treatment instituted. Even massive induration of the entire lung on one side may for many years give rise to no other symptoms than cough and mild dyspnea on exertion.

In fibrosis following pneumonia, both lobar and lobular, the prognosis is not so good, as it renders the individual decidedly susceptible to acute bronchial and pulmonary, particularly tuberculous infections. In tuberculosis, fibrosis is a protective and conservative process with a tendency to limitation rather than dissemination of the infection; hence with a favorable environment even these patients may enjoy many years of useful existence. Numerous and large bronchiectatic cavities with purulent expectoration and a febrile state render the prognosis unfavorable. Acute tuberculous or other infections occurring in an individual suffering from pulmonary cirrhosis, because of lowered resistance, are usually serious in their consequences.

When in advanced fibrosis signs and symptoms of cardiac decompensation appear, the prognosis is grave, as it is seldom possible to restore cardiac competency when once this is lost.

Pathology.—The morbid changes vary with the cause, the extent and the localization of the process. Usually two varieties are distinguished:

(*a*) the massive; (*b*) the disseminate or insular. The massive type of the disease is usually unilateral. The affected lung is much diminished in bulk and retracted toward its root. The chest of the affected side is flattened, angular and sunken. The lung is grayish white, or deeply pigmented, and greatly resists cutting. Numerous bronchiectatic cavities may be present. Pleural adhesions may be extremely dense, and render removal of the lung difficult. The organ itself is airless, firm, and, on section, shows bands of fibrous tissue extending from the hilus to periphery. There is marked peribronchial and perivascular fibrosis. The pleura is found greatly thickened, especially in the pleurogenous type, and is firmly adherent, often completely obliterating the cavity. In pulmonary fibrosis, the result of compression by pleural exudates or tumors, the pleura, although markedly thickened, shows fewer adhesions. The opposite lung is markedly emphysematous, and the heart is displaced

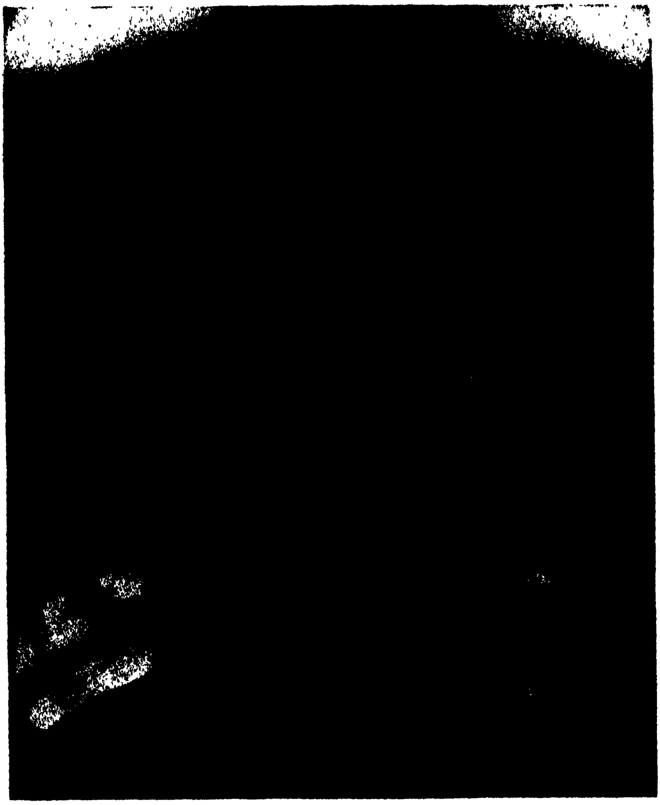

FIG. 4.—PULMONARY SCLEROSIS, THE RESULT OF THE INHALATION OF FLOUR DUST. Note enlargement and thickening of bronchi.

toward the affected side. The liver and stomach are drawn upward with the diaphragm on the affected side; in severe cases mediastinal displacement may be observed.

The disseminate or insular type is usually bilateral and develops as a sequence of bronchopneumonia, chronic bronchial disease, pneumonoconiosis, brown induration, pulmonary syphilis and tuberculosis. The lung tissue is firmer and denser than normal; it presents grayish nodules on its cut surface. Following bronchopneumonia, the terminal bronchioles and the alveoli may be found obliterated by fibrous tissue. Emphysematous areas may be found interspersed among the sclerotic ones. If the productive inflammation follows bronchitis and pneumonoconiosis, the sclerotic tissue is distributed chiefly along the bronchial tree.

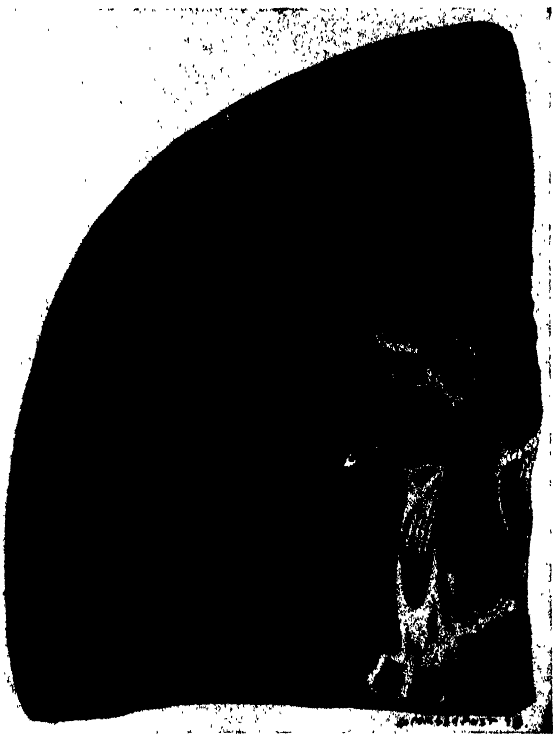

FIG. 5.—GROSS DRAWING OF ANTHRACOTIC LUNG. Note the peribronchial lymph-nodes filled with carbon. (McJunkin.)

In tuberculosis the cirrhosis may be localized or appear widely disseminated throughout the greater part of both lungs. Caseated and calcified areas and cavities may be found in the affected parts. It should be remembered that extensive tuberculous fibrosis of the lung may be present without other gross evidence of the disease.

Definite gummata, irregularly scattered throughout the lung, caseous nodules, hyalin degeneration, and areas of fibrosis proceeding usually from the root of the lung, are findings in pulmonary syphilis in the adult.

Advanced cirrhosis of all types is invariably attended by marked obstruction of the pulmonary circulation, leading to right ventricular hypertrophy.

PNEUMONOCONIOSIS

Under this term are classed all forms of pulmonary fibrosis occurring as a result of the inhalation of dust, both organic and inorganic. It is decidedly an occupational disease and, outside of mining and large industrial districts, is rather rare.

Etiology.—The lung tissue proper is fairly well protected from ordinary amounts of dust, such as obtain in large cities, by the action of the ciliated epithelium, phagocytes, mucous secretions and cells of the bronchial tubes. In individuals, however, who work in atmospheres heavily laden with dust these protective mechanisms are insufficient, and deposition of the particles in the epithelium occurs. Epithelial destruction and desquamation permit their entrance into the lymph stream, where they are carried to the peribronchial and mediastinal lymph-nodes, connective tissue structures, perivascular tissues, and even distant organs, all of which leads to definite pathologic changes in these structures. The most common forms of pneumonoconiosis are:

(*a*) Anthracosis, from inhalation of coal-dust. This is found most commonly in coal miners and workers in coal yards, docks, etc.

(*b*) Siderosis, from inhalation of iron and steel dust by metal grinders and polishers, nail makers, file makers, etc.

(*c*) Chalicosis, from inhalation of stone-dust by stone-workers, such as quarry laborers, potters, grinders, plasterers, and porcelain makers.

(*d*) Accumulation of iron and stone-dust, found principally in grinders, particularly those using dry stones.

According to Oliver, gold miner's phthisis is exceedingly common in South Africa. The fibrosis is so extensive and of such rapid development that the occupation of mining gold on the Rand can be followed but a limited number of years. Slag dust, a name applied to the powdered refuse from blast furnaces, produces a peculiar pulmonary condition resembling pneumonia, and giving rise to almost identical symptoms and signs. Vegetable dust may lead to similar affections. Workers in grain elevators, flour mills, woolen mills, cotton mills, furniture factories and tobacco factories may suffer to some extent from pathologic changes identical to but less pronounced than those produced by metal and mineral inhalation.

The susceptibility of workmen to the same kinds of dust varies greatly. Some, after years of exposure, show little or no sign of impairment of health, while others succumb comparatively early to the pulmonary changes produced. Unsanitary and unhygienic environment and faulty nutrition are probably factors in the early development of the changes.

Symptomatology.—CLINICAL HISTORY.—The clinical symptoms depend upon the cause, the extent, and the duration of the process. The inhalation of metal or stone-dust is apt to lead to symptoms earlier than that of coal-dust. In most instances symptoms incapacitating the individual do not develop until after years of exposure. In general, symptoms of chronic bronchitis are the earliest to appear. The cough at first is unproductive but later expectoration, stained gray, black or red, containing the material inhaled, occurs. Microscopic examination shows the offending particles free and in the cells with which the sputum abounds. When bronchiectatic cavities have formed, the sputum becomes profuse and purulent. Long-continued cough leads to pulmonary emphysema with dyspnea and asthmatic symptoms. The wheezing and shortness of breath may constitute the predominating features of this condition. In advanced stages pulmonary emphysema and fibrosis lead to symptoms of impaired pulmonary circulation, right ventricular incompetence, and general circulatory failure, as in emphysema and fibrosis from other causes.

PHYSICAL FINDINGS.—The physical signs are those of chronic bronchitis, pulmonary emphysema, fibrosis and bronchiectasis. In the earlier stages only the signs of chronic bronchitis prevail. Later respiratory movements become restricted, the patient appears in respiratory distress, especially upon exertion. The typical barrel-shaped chest of ordinary emphysema is absent, although some hypertrophy of the accessory respiratory muscles may be evident.

Right ventricular incompetency is manifested by epigastric pulsation, distended veins and edema. Vocal fremitus and the percussion note become impaired only when marked induration and bronchiectatic cavities have developed.

Auscultatory findings vary with the development of the disease. Coarse mucous bronchial râles are present in the earlier stages; later, bronchovesicular and bronchial breathing with sibilant râles, expiratory prolongation and the characteristic wheezing sound of the asthmatic develop.

In bronchiectasis and secondary tuberculous infection with formation of cavities the usual signs of vomicæ are present.

Diagnosis.—This is based upon the history of long-continued exposure to a dust-laden atmosphere, and subsequent development of symptoms and signs. Careful and repeated examinations of the sputum are necessary, not only for the purpose of detecting particles of stone, steel, iron, or coal, but to exclude tuberculosis—the symptoms and signs of which are essentially identical, and which may have become engrafted upon a pneumonoconiosis.

Treatment.—The condition once well advanced is not amenable to treatment. *Preventive measures* are, therefore, important. Pneumonoconiosis is distinctly an occupational disease: hence the problem is largely an industrial one. Proper ventilation of workshops and mines, and a reduction in the number of working hours have materially lessened its prevalence. General **hygienic measures**, such as proper housing, a plentiful supply of sunlight and fresh air in the house, personal cleanliness and proper nutrition, are important.

Employers are realizing to-day more than ever the fact that the efficiency of the workman is directly proportional to his health, and that it is to their own interest to guard and conserve this valuable asset.

When severe bronchial irritation appears, a **change in occupation** should be advised. Expectoration should be increased as much as possible by stimulating or nauseating **expectorants**, such as **ammonium chlorid or carbonate, apomorphin, ipecac and antimony**. Inhalations of **wine of ipecac, terpin hydrate, oil of sandalwood** and **oil of eucalyptus** in the form of a continuous spray are valuable.

In advanced stages of the disease, treatment must be directed toward amelioration of the symptoms of bronchitis and emphysema and to maintenance of proper nutrition and conservation of cardiac competency.

Prognosis.—Removal of the patient from the causative influences in the early stages will undoubtedly lead to an arrest of the process. Where a change of occupation is impossible, the prognosis may be favorably influenced by careful attention to ventilation, general hygienic conditions and the use of respirators. The prognosis is decidedly better in anthracosis than in siderosis and chalicosis or a mixture of the latter two. The amount of dust inhaled is an important factor. Grinders and polishers working with wet stones are less severely affected than those working with dry stones. In the advanced stages the prognosis is decidedly unfavorable, as neither the removal of the cause nor any method of treatment will influence the fibrosis which has occurred, and which exhibits a tendency to progression.

The influence of pneumonoconiosis as a predisposing factor in the development of tuberculosis has been much discussed.

Osler, citing the figures of Wainwright, states that in Scranton, Pa., in the anthracite district only 3.37 of the male mine workers suffer from tuberculosis, while in those of other occupations the percentage is 9.97 per cent. On the other hand, statistics compiled by Miss Lillian Brand from the U. S. Census Report of 1900, and graphically portrayed in the "Handbook on the Prevention of Tuberculosis," show that marble- and stone-cutters head the list of fifty-three occupations in the death rate from tuberculosis. Metal and mineral dust is conceded to be more irritating than coal dust, and therefore more apt to predispose to tuberculosis. Mr. A. J. Lonza, in discussing miner's consumption in the Joplin district, states that of 720 miners examined, 433, or 60 per cent., showed definite signs of lung injury, 103 of whom had tubercle bacilli in the sputum.

Pathology.—The morbid changes found are essentially the same in all forms of the disease; they consist in the deposit of the particular material inhaled and an overgrowth of fibrous tissue from irritation. The degree of alteration is dependent upon the nature, duration and quantity of the irritant. The color of the lung varies with the kind of dust inhaled. In anthracosis, it is slate-colored or black; in siderosis, red; in chalicosis, gray; and in ultramarine inhalation, blue. The lung appears mottled, dark gray or black in color, and the pleural surfaces may be adherent. The cut surface is smooth, dense, cuts with resistance and a dark fluid exudes from the surface. There are areas of fibrosis and of emphysema, dilated bronchi and occasional cavities. The peribronchial and mediastinal lymph-glands are pigmented, sclerosed and enlarged. The bronchi display the thickening and degeneration of chronic bronchitis. The epithelium of the bronchioles and alveoli is granular, pigmented and desquamating. Pigment-bearing leukocytes are abundant in the sputum. The dust particles deposited in the bronchi and alveoli are carried by the lymph stream and leukocytes to the bronchial and mediastinal lymph-glands and to the connective tissue septa between the secondary lobules, where the fibrosis becomes most pronounced. Pigment has been found in the liver and other organs.

In siderosis, hard, gritty, dark gray nodules are formed in the lung which may soften and lead to expectoration of masses of silicate material (pneumoliths).

EMPHYSEMA OF THE LUNGS

Pulmonary emphysema is a condition characterized by abnormal atrophy of alveolar walls, dilatation and rupture of alveoli, loss of elastic recoil, and a state of permanent inspiratory expansion of the lungs.

Etiology.—AGE.—The disease, although most prevalent after middle life, does occur in children. The most profound example of emphysema ever seen by the author was in a child of eight years of age suffering from asthma. In children it not infrequently develops as a sequel to measles, whooping-cough and bronchopneumonia. These cases manifest a decided tendency to return to practically normal conditions upon recovery from the primary disease.

HEREDITY.—Although heredity is believed by some to be a factor in the production of emphysema, its influence can be but a minor one, and is manifest in only a limited number of sufferers.

SEX.—The disease is decidedly more common in males than in females. This predominance in men can be ascribed only to the deleterious influences of occupation, and at once stamps it as an industrial affection.

OCCUPATION.—All occupations involving severe and continuous muscular effort, especially heavy lifting, predispose to emphysema. It is a disease of the hard-working classes in which continued and excessive respiratory effort is required. It is quite frequent in musicians playing wind instruments and in glass-blowers. All individuals whose occupation involves exposure to sudden and severe changes in temperature, predisposing them to recurrent attacks of bronchitis, are prone to develop emphysema. To this class belong cab drivers, teamsters and street laborers and workers in dusty atmospheres. All sufferers from pneumonoconiosis, because of the presence of chronic bronchitis, of the type involving the smaller bronchi, are common sufferers from emphysematous changes.

Symptomatology.—CLINICAL HISTORY.—The symptoms, as a rule, develop gradually; years may elapse before marked subjective symptoms become manifest. Symptoms most commonly develop in the middle or advanced periods of life, although they may be found present in early childhood. The first complaint is breathlessness on exertion. Dyspnea, as the disease progresses, becomes more pronounced, until in the fully developed stage it appears constant even in repose. It is distinctly expiratory in type, the lung being in a state of permanent inspiratory expansion. The dyspnea is not characterized by labored and forceful respirations, but rather by an inability to empty the lungs of air, because of loss of pulmonary elasticity, and fixation of the thorax.

Cough and other symptoms of bronchitis may precede the dyspnea for a considerable period, and harass the patient to the end of his life. In the earlier stages the cough is a winter cough, disappearing during the warm weather. Dyspnea is always aggravated by bronchitis and attacks closely simulating asthma may be occasioned by it. Genuine bronchial asthma is commonly associated with emphysema in the rôle of a causative factor. In the advanced stages cough frequently becomes a constant symptom, and contributes much to the distress of the sufferer. The sputum differs little from that of ordinary bronchitis except when bronchial asthma is present, when it contains eosinophilic cells, Charcot-Leyden crystals, and Churchman's spirals.

The cyanosis is much more pronounced than the other symptoms would indicate, and except in congenital heart disease is never found in the same degree in patients able to be up and about. Symptoms referable to disturbed circulation invariably develop in advanced types of emphysema. Distention and rupture of alveoli compromise pulmonary circulation, the work of the right ventricle is increased, and hypertrophy occurs. The second pulmonic sound is accentuated. With increasing resistance to pulmonary circulation, dilatation, relative tricuspid insufficiency and decompensation of the right heart occur. The cough, dyspnea and cyanosis become more pronounced. The veins become over-distended with blood; those in the neck may pulsate forcibly with each ventricular contraction. The arteries are poorly filled; the pulse small and weak; systolic and diastolic pressures low; temperature subnormal. The liver enlarges from congestion and may pulsate. There is passive congestion of the stomach and intestines with digestive disturbances; passive congestion of the kidneys with scanty highly colored urine containing albumin and casts; and engorgement of the systemic veins with general edema. Hemoptysis and hematemesis may occur. The patient finally succumbs to circulatory and nutritional failure.

PHYSICAL FINDINGS.—*Inspection.*—The appearance of the patient is characteristic. The facial expression is one of distress. The skin and mucous membranes are cyanotic, the lips thickened, eyes prominent and superficial veins distended. When nutrition is markedly interfered with, clubbing of the fingers and toes may be seen. The patient is rarely recumbent and often orthopneic. Litten's sign is usually absent. The chest is rounded in contour, barrel-shaped, its anteroposterior diameter being increased. The shoulders are rounded, the dorsal spinal curve exaggerated, the sternum and clavicles prominent and the ribs horizontal. The increase in the anteroposterior diameter is more apparent in the upper than the lower regions of the thorax. The accessory muscles of respiration, such as the sternomastoids and scaleni, are hypertrophied and tense, drawing the head forward toward the sternum. The neck appears greatly shortened and thickened, and clavicular and intercostal spaces are bulging.

The respiratory movement is much restricted, there being little expansion but rather a lifting up of the thorax in its entirety. The expiratory phase is much prolonged and during inspiration there may be distinct depression of the lower regions of the thorax. Marked epigastric pulsation is frequently seen, while the normal apical impulse is absent.

Palpation.—Palpation confirms inspection as to restriction and abnormality of respiratory movements. Vocal fremitus is usually diminished. The normal apex beat is palpated with difficulty, while marked pulsation may be felt in the epigastrium.

Percussion.—The percussion note is hyperresonant; the area of pulmonary resonance is increased, encroaching upon the normal hepatic, splenic and cardiac dullness. It is not uncommon to find resonance as low down as the twelfth rib posteriorly and the seventh rib anteriorly. Careful percussion of the lower pulmonary borders indicates the restriction of pulmonary excursion during respiration. The area of absolute cardiac dullness is much diminished, and the size of the heart outlined with difficulty in consequence. Even a greatly enlarged heart may be so completely covered by the emphysematous lung that it is impossible to determine its outline. Liver dullness is restricted; splenic dullness may be entirely absent. The diaphragm is depressed and its excursions limited.

Auscultation.—Breath sounds are enfeebled and the expiratory sound distinctly prolonged, so that its duration may be three or four times the length of that of inspiration. When primary or secondary asthma is present, the expiratory act is accompanied by marked wheezing or whistling sounds and râles of varying caliber. Moist bronchial râles are present if there is bronchitis; and crepitant or crackling râles at the lung bases when there is edema. A distinct muscle sound often mistaken for pleuritic friction is frequently heard, especially over the upper portion of the chest. Genuine pleuritic friction sounds, however, are also present in some cases. The heart sounds are indistinct owing to the interposition of lung tissue between this organ and the chest wall. There is present increased pulmonary tension, and accentuation of the second pulmonic sound. Relative tricuspid insufficiency gives rise to a systolic murmur transmitted upward along the left margin of the sternum. In other cases there is simply a reduplication of the first sound, or the first sound may be exceedingly weak, short and devoid of all muscle elements. Spontaneous pneumothorax gives rise to the usual physical findings of this condition.

Diagnosis.—The diagnosis of a well-developed, large-lunged emphysema presents little or no difficulty. The distressed and cyanotic appearance of the patient, the shape and contour of the chest, expiratory difficulty and findings upon physical examination are quite characteristic. The history of asthma or chronic cough, the occupation, and in children an antecedent pertussis or an attack of measles are important in the diagnosis of the earlier stages. The same degree of cyanosis is seldom witnessed in other diseases. It should be remembered that a "barrel-shaped" chest does not necessarily mean high grade emphysema, and that emphysema (atrophic) may be present in contracted chests.

DIFFERENTIAL DIAGNOSIS.—(*a*) *Pneumothorax.*—This is distinguished by its acute onset, with pain in the side, dyspnea and shock. The condition is unilateral and there is marked displacement of the heart to the opposite side. The percussion note is highly tympanitic; if fluid is present there are splashing sounds and a metallic tinkle. Evidence of tuberculosis is present in the majority of cases. Spontaneous pneumothorax is not uncommon as a complication of emphysema of the lungs.

(*b*) *Pulmonary Tuberculosis.*—In pulmonary tuberculosis with the characteristic "phthisical" chest, differentiation is easy. When, however, tuberculous disease develops in an emphysematous lung, its recognition is often difficult, particularly on the basis of physical findings; and the diagnosis rests upon the presence of fever and tubercle bacilli in the sputum.

(*c*) *Primary Cardiac Disease with Decompensation.*—This resembles emphysema in the dyspnea and cyanosis. The differentiation is made by the history of previous disease; the presence of cardiac disease prior to the development of dyspnea; the absence of expiratory dyspnea; the physical findings of emphysema and the prominence of the cardiac impulse and murmurs.

(*d*) *Asthma.*—Asthma and emphysema frequently coexist. The history will usually disclose which is the primary affection. Pure bronchial asthma most frequently develops in early life. If asthma develops late it is usually secondary to other pulmonary or cardiac disease.

The roentgenogram is an important aid in differential diagnosis.

Complications and Sequelæ.—These are pneumothorax, asthma, interstitial emphysema, tuberculosis and cardiac decompensation. Emphysema of the lungs is frequently associated with chronic bronchitis, asthma, cirrhosis of the lung and pneumonoconiosis. The compensatory types occur with all conditions, seriously interfering with the functional activity of any considerable part of the lung.

Clinical Varieties.—These are described as (1) compensatory; (2) hypertrophic; (3) atrophic; (4) acute vesicular; (5) interstitial.

(1) COMPENSATORY EMPHYSEMA.—This is localized emphysema, the result of pulmonary disease, such as tuberculosis, fibrosis of the lung, atelectasis, tumors and compression of one lung by pleuritic effusions. It may involve an entire lung or only circumscribed portions of it. It is a physiological process compensatory to the loss of function of lung tissue; it may be transient or become permanent. If permanent, atrophy of the alveolar walls and fusion of air vesicles takes place, as in the hypertrophic or large-lunged variety.

(2) HYPERTROPHIC OR LARGE-LUNGED EMPHYSEMA.—In general, when the terms vesicular emphysema or pulmonary emphysema are employed, this is the type one has in mind. It is characterized clinically by marked alterations in the form and contour of the chest, expiratory dyspnea and cyanosis; and pathologically, by atrophy of the alveolar walls, distention and rupture of air vesicles, and circulatory disturbances.

(3) ATROPHIC EMPHYSEMA.—Atrophic emphysema, also termed senile or small-lunged emphysema. This is primarily an atrophic condition of the lungs, incidental to atrophic changes occurring elsewhere in the body as a result of senility. There is the same atrophy and dilatation of alveoli as in the hypertrophic variety, but the lungs are small, and the thorax contracted, rigid, and wasted. The area of absolute cardiac dullness is normal, or perhaps increased, and the sternocostal angle is oblique. The septa are atrophied, the alveoli ruptured, and bullæ of considerable size form. The lungs collapse readily on opening the chest, and appear pigmented. The bronchi are dilated, their walls thinned, and the mucous membrane shows evidence of chronic inflammation. Collapse, edema, and infarction may be found, especially in the lower lobes. Clinically, chronic cough, dyspnea, respiratory limitation, atrophy and emaciation are the chief features.

(4) ACUTE VESICULAR EMPHYSEMA.—This is an acute over-distention of the air vesicles, occurring as the result of acute obstruction of the bronchioles through spasm, inflammatory tumefaction or exudation. In narrowing of the bronchioles from any cause, more air enters the alveoli than can escape; and as the alveolar walls are decidedly elastic, dilatation results. This occurs most commonly in acute asthma, acute bronchitis, asphyxia, and sudden collapse of any considerable portion of the lung. Repeated attacks of asthma may lead to permanent alveolar distention and typical hypertrophic emphysema. In most instances of acute vesicular emphysema, however, recovery or death occurs before permanent dilatation of the alveolar sacs takes place; hence the pathologic change, characteristic of true emphysema, is absent. The condition is manifested by dyspnea, increased pulmonary volume, hyperresonance, and the adventitious sounds, usually present in asthma and acute bronchitis.

(5) INTERSTITIAL EMPHYSEMA.—This consists in the escape of air from ruptured alveoli into the surrounding interlobular connective tissue. The margins of the lung are most commonly the seat of this infiltration. It appears postmortem as blebs or bullæ, slightly elevated above the

surrounding lung tissue, and capable of displacement by pressure. The blebs may rupture, producing pneumothorax, infiltration of the mediastinal space or of the connective tissue of the neck. The causes of this condition are (*a*) those which lead to violent expiratory effort—such as whooping cough, asthma, foreign bodies in the trachea or bronchi; (*b*) penetrating wounds—such as stab wounds, tracheotomy wounds, fractured ribs puncturing the lung, and penetrating bodies in the esophagus; (*c*) pathological processes leading to pulmonary rupture—such as abscess, gangrene, tuberculosis, tumors or infection with gas bacillus; (*d*) great increase in the intrapulmonary tension such as occurs in the violent physical effort of straining in childbirth, etc.

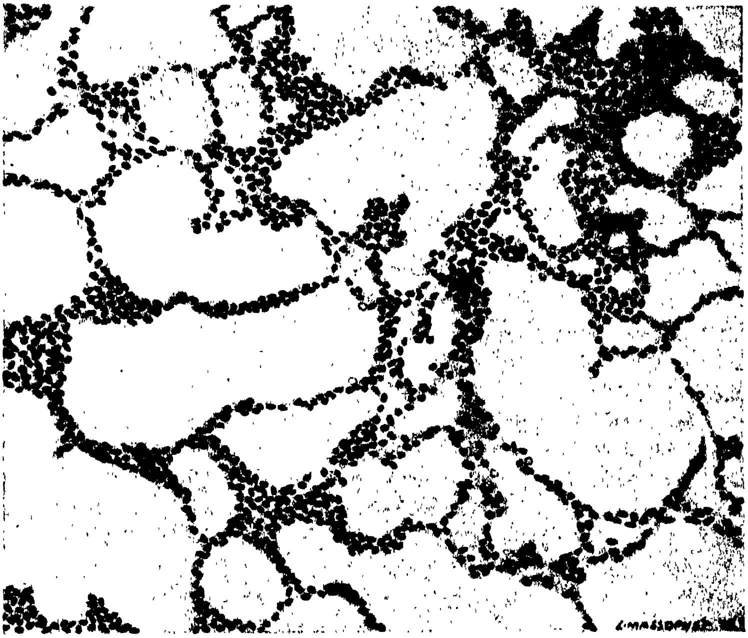

FIG. 6.—LOW POWER CAMERA LUCIDA DRAWING OF LUNG IN BRONCHIAL ASTHMA VESICULAR EMPHYSEMA. (McJunkin.)

Unless infiltration of the tissues of the neck or spontaneous pneumothorax occurs clinical evidence of interstitial emphysema will be absent, and the diagnosis is usually made postmortem. Hyperresonance, if present, does not distinguish this from the vesicular type of emphysema.

Treatment.—This is best discussed as: (1) prophylactic; (2) palliative; (3) treatment of complications.

1. PROPHYLACTIC.—The alveolar atrophy, circulatory changes, and

loss of elastic tissue in advanced emphysema are progressive and permanent, and are but feebly influenced by any therapeutic measure. Prophylaxis, therefore, is of prime importance. Sufferers from chronic bronchitis and asthma should be warned of the danger of emphysema, and of the certainty of its development, if these attacks recur frequently. They should **avoid exposure** to cold, wet, and sudden changes of temperature. If possible, a sojourn in winter in a warm, equable **climate** is to be recommended. Often a permanent change of climate is necessary. **Dusty and irritating atmospheres should be avoided.** Obstructions and other lesions of the upper respiratory tract should be removed as they predispose to asthma and bronchial infections. For similar reasons all oral, tonsillar, and sinus infections should be carefully dealt with. Those suffering from hay-fever or asthma should seek a region free from pollen during the season of its prevalence. Hydrotherapeutic measures such as the cold sponge, shower, or plunge are of value in reducing the patient's susceptibility and reaction to changes of temperature and respiratory infections. All **unnecessary increase of intrapulmonary** tension, such as occurs in violent exercise and heavy lifting, **should be avoided.** Occupations such as glass-blowing and the playing of wind instruments should be abandoned. The **diet** should be regulated so as to avoid gaseous distention; the **bowels** should be kept **well regulated.**

2. PALLIATIVE.—When circumstances do not permit the removal of the patient from conditions productive of emphysema, our efforts should be directed toward minimizing the evil effects of these conditions. Bronchitis and asthma should be treated in the hope of lessening the cough and intra-alveolar tension. Every effort should be made to protect the patient from dust and other substances which irritate the bronchial mucosa. The **hygiene** of the home as well as the work-shop requires careful investigation and attention. Plenty of fresh air, sunshine, rest and nourishing food must be provided, and the patient's general health and resistance guarded to the utmost.

Various **exercises,** physical methods, and mechanical appliances have been used for the relief of the symptoms of emphysema, and for the purpose of reducing the volume of the distended lung. Respiratory exercises carried out for the purpose of increasing the volume of air expelled from the lungs during expiration have produced gratifying results. Hofbauer advises that the patient be instructed to fix his attention upon expiration and by the proper use of his abdominal muscles be trained to more effectually empty his lungs. He has also devised a mechanical contrivance to aid the patient in this effort. It consists of an abdominal binder having on its inner side a large rubber bag which is rhythmically inflated from a tank containing compressed air. The effect of such exercises can be enhanced by massage of the chest and abdominal muscles, also by mechanical devices, such as those of Rossbach and Boghean, which serve to compress the bony thorax during expiration. In the absence of any such mechanical device, mild compression of the chest by the patient himself or by an assistant will serve a similar purpose.

Physical methods, such as expiration into rarefied air, inhalation of compressed air, and exhalation into rarefied air, and the use of the differentiator, all have found supporters, while the value of each has been questioned. That the field of usefulness for all such mechanical devices is limited is certain, for they are seldom within reach of the class most frequently affected. Furthermore, in advanced cases of emphysema, the use of mechanical devices for violent compression of the thorax may be a source of danger to atrophied alveoli and cardiac integrity, and should be avoided. **Hydrotherapeutic** measures, such as hot and cold douches, the cold sponge and pack, exert a favorable influence upon the circulation, and are of value when intelligently used in conjunction with other hygienic and palliative measures. W. A. Freund advocates resection of the costal cartilages for the relief of thoracic rigidity and fixation; he bases his conclusions upon the theory that primarily there is a disease of these structures with lengthening of them and enlargement of the thoracic cavity. The pulmonary distention he regards as secondary.

Chronic bronchitis and asthma may be much relieved by **tonics** and **expectorants**; of the former, **nux vomica** or **strychnin** is of distinct value, if administered over long periods of time. **Iron** and **arsenic** are useful in selected cases. **Potassium iodid** in small doses is without doubt a most serviceable medicinal agent. In exacerbations of bronchitis, the ammonia preparations, **ipecac, apomorphin,** and, if necessary, **heroin** or **morphin,** should be employed to allay the cough. **Inhalations of mineral waters, tincture of benzoin** and **guaiacol** in vaporized form have been recommended, also **oily sprays of menthol, eucalyptol,** and **terebene.** Asthmatic attacks should be controlled as promptly as possible; in the interval **strychnin** and **potassium iodid** should be administered. Some form of surgical treatment may be indicated.

3. TREATMENT OF COMPLICATIONS.—Complications requiring treatment are chiefly cardiac. When these develop they require the same management as does cardiac insufficiency from any cause. Absolute **rest in bed** is essential. **Strychnin** and **digitalis** are indicated, the dosage to be regulated by the degree of cardiac asthenia and the tolerance of the patient. **Caffein** and **diuretin** are of service when there is edema. It is to be remembered that when once cardiac compensation is broken in emphysema, it is restored with difficulty. When cardiac decompensation is manifested by a severe dyspnea and cyanosis, **venesection** must be resorted to for immediate relief.

Prognosis.—Although emphysema is a chronic and incurable condition, much can be done to relieve the patient and prolong life. It may not completely incapacitate the individual nor seriously threaten life until advanced age is reached. The earlier in life marked evidence of emphysema develops, the graver the prognosis. Early removal of obstructions and irritative lesions of the upper respiratory tract lessens the tendency to asthma and bronchitis, and renders the prognosis more favorable. Hard labor, changeable climatic conditions, work in dusty atmospheres, and the inordinate use of the vocal organs favor progression of emphysematous changes. Frequent asthmatic paroxysms incapacitate earlier and increase the liability to cardiac incompetency.

A rapid pulse, dyspnea, cyanosis and edema indicate a failing heart and probably a fatal issue.

Pathology.—Upon opening the chest the lungs appear distended and fail to collapse. They are paler than normal and their margins approximate, covering the pericardium. The sternum is displaced forward and upward, and the ribs appear horizontal. The pleura is dry and pale; the costal cartilages are found calcified. The organ is apt to pit on pressure, even in the absence of edema, is soft, and does not crepitate upon palpation as does normal lung tissue. Along the lung margins numerous blebs may be seen, representing coalesced and distended air vesicles, or accumulations of air in the interstitial connective tissue. Pleural adhesions are common. Upon section the organ appears spongy, paler than normal, and the enlarged vesicles are readily visible to the unaided eye. The bronchial mucosa is thickened and congested; bronchiectatic cavities are common. Microscopical examination shows individual alveoli enlarged; others, with ruptured septa, united to form bullæ of varying sizes. There is marked atrophy, and destruction of alveolar walls with consequent atrophy and disappearance of blood-vessels and imperfect aëration of the venous blood. The atrophy is said to involve particularly the elastic tissue, so that in advanced cases only indistinct fragments of this tissue remain. This, however, has been denied by more recent investigators (Sudsuki). In the senile type the lungs are smaller than normal, collapse readily; and the bullæ may be so numerous and large as to occupy the greater part of the entire lung.

The marked encroachment upon capillary capacity, together with varying intrathoracic pressure, constitute a decided strain upon the right ventricle to which the organ responds by hypertrophy. Hence enlargement of the right heart is usually found in advanced emphysema. When cardiac failure has occurred, passive systemic congestion is manifest.

Pathogenesis.—Many theories concerning the pathogenesis of vesicular emphysema have been advanced. It is conceded by most writers that underlying its development is a *weakness of pulmonary tissue,* inherited or acquired, which permits of loss of elasticity of the lungs upon repeated over-distention. The nature of this fundamental weakness has not been determined. Cohnheim believed that it is a developmental defect in the elastic tissue elements; others view it as a disorder of nutrition. It is upon the basis of such fundamental defects that most emphysemas, particularly those occurring in young children and those following acute infections, associated with violent cough, can be explained. Strümpell emphasizes the loss of pulmonary elasticity as the important and predominating factor in all cases; he compares emphysematous lung tissue to an old gum elastic band, which through repeated and excessive stretching has suffered elastic fatigue. Emphysema is, therefore, a permanent inspiratory distention of the lung from which a return to normal expiratory collapse is impossible; hence the organ maintains this state even after its removal from the body. Furthermore, loss of pulmonary elasticity is a constant feature of advancing age, and constitutes but a part of the same change in other tissues of the body.

An important factor in the production of pulmonary emphysema is increased *intravesicular tension.* This may be brought about by forced inspiratory or expiratory .efforts. The *inspiratory* hypothesis first advanced by Laennec is considered by most authors insufficient explanation of the production of general emphysema, and has been subordinated to the expiratory theory. Permanent obstruction of a bronchus or bronchioles by tumors, foreign bodies or inflammatory exudate with collapse of a portion of the lung may, however, result in a compensatory emphysema of the adjacent lung tissue, through inspiratory over-distention. Normally inspiration is the active and expiration the passive phase of respiration. The latter is accomplished mainly through the elastic force of the lungs. If this is diminished or lost, the amount of residual air is increased and inspiratory distention results. Investigations by Schall and Bruns indicate that increase of residual air in itself is insufficient to produce the changes characteristic of emphysema and that at least two factors enter into its production, namely, defective elastic tissue and over-distention. The over-distention of the alveoli occurs most frequently in chronic bronchitis and asthma. In the act of coughing there is first a deep inspiration. This is followed by closure of the glottis and a violent expiratory effort forcing the air through a partially relaxed glottis. As a result the alveoli are over-distended, particularly those in the apices and margins of the lungs which are inadequately supported by the thoracic walls. The primary changes are, therefore, found in these parts. Frequent repetition of this will eventually destroy the elastic recoil of pulmonary tissue, and permanent inspiratory expansion results. In bronchial asthma there is besides the cough an additional factor of importance. Bronchial obstruction, either through spasm or exudate, interferes more with expiration than inspiration; the residual air is in consequence greatly increased and the lungs distended.

That the *expiratory* factor is important in the production of emphysema is indicated by the fact that most asthmatics develop emphysema to a decided degree.

Chronic Bronchitis and Asthma.—The association of emphysema with chronic bronchitis and asthma is so common that it cannot be regarded as accidental. Both conditions are associated with more or less obstruction of the finer bronchioles by exudate or spasm. This leads to excessive expiratory efforts, cough and prolonged and forcible expiration, where the elastic recoil of the lung is aided by the accessory muscles of respiration. These violent efforts at expiration result in permanent alveolar distention. *Whooping-cough* and *measles* are considered causes of emphysema. In these diseases, as in asthma and bronchitis, two factors are operative: (*a*) bronchial obstruction; and (*b*) undue expiratory efforts. In permanent emphysema following measles and whooping-cough, impaired alveolar nutrition is probably also an important factor.

In *violent muscular effort,* especially in heavy lifting, the mechanism of increasing intrapulmonary tension is similar to that engaged in the act of coughing or straining, and may lead to identical changes.

Finally, the view of W. A. Freund deserves mention. According to his theory there exists disease of the costal cartilages and ribs, with lengthening of these structures and fixation of the thorax in the position of inspiration. The pulmonary changes are regarded as secondary. He himself did not, however, find these changes in all cases of emphysema. By others they are regarded as secondary rather than primary.

In pulmonary emphysema there is an *increase of residual air* in the lungs. The mid-capacity is increased, the vital capacity decreased, and the functional dead space is increased (Hewlett). Hoover states that the increase in dead space is best explained by bronchiolar atony, viz., an elongation and broadening of the bronchioles.

PULMONARY ABSCESS AND GANGRENE

Pulmonary abscess and pulmonary gangrene are so similar in their etiology, pathology and clinical manifestations that their consideration in the same chapter appears desirable.

Etiology.—In general the same etiologic factors may be operative in both abscess and gangrene of the lung. Primary suppuration in the lung rarely, if ever, occurs. The process is an infectious one, implanted upon tissues previously damaged by disease, trauma or circulatory derangement. The organisms responsible for the distinctive lesions are most commonly pus cocci, although it cannot be denied that virulent pathogenic organisms may produce necrosis and suppuration. The most frequent type of lung abscess is the tuberculous. Invasion of pulmonary tissue by *Actinomyces bovis,* oïdium and aspergillus fungi, echinococcus, the lung fluke, *Bacillus mallei* and *Spirochæta pallida* may result in abscess. The pneumococcus and influenza bacillus are frequently found in association with pus organisms in these lesions.

Numerous microörganisms, none of which can as yet be regarded as specific in the production of gangrene, have been described. Their destructive and putrefactive action depends perhaps mainly upon their association with pathogenic bacteria and the nutritional changes induced by the invasion of these organisms. Necrosis in itself does not constitute gangrene, but the necrotic area provides a fertile field for invasion by saprophytic and putrefactive bacteria without which there can be no gangrene. The most frequent causes are:

(1) Lobar Pneumonia.—Abscess is comparatively infrequent as a complication of this disease. In 1200 cases of lobar pneumonia observed by Frankel, less than 2 per cent. developed abscess. Postmortem, many cases of purulent infiltration are classed as abscess. In a considerable percentage of these cases complete resolution would have occurred had the patient survived the pneumonia. Chronic alcoholism, general en-

feeblement from any cause, and diabetes, predispose to abscess. Gangrene is even less frequent as a complication of lobar pneumonia. Frænkel found it in but 4 per cent. of his cases; while Aufrecht did not observe a gangrenous process in over 1500 cases of croupous pneumonia. Abscess may precede the development of gangrene.

(2) BRONCHOPNEUMONIA.—Most cases of abscess or gangrene developing in the course of bronchopneumonia are said to be due to the aspiration of pyogenic or putrefactive organisms into the finer bronchi. Such complications are particularly apt to occur when putrid bronchitis or bronchiectatic cavities are present. Bronchopneumonia in those enfeebled from age and bronchitis, and in infants suffering from malnutrition, predisposes to abscesses and gangrene. The writer has observed a pulmonary abscess in a child of three months suffering from inanition and bronchopneumonia.

(3) FOREIGN BODIES.—Aspiration of infectious material and foreign bodies into the bronchi is one of the most common causes of both abscess and gangrene. Such an accident is especially apt to occur during periods of unconsciousness from general anesthesia, alcoholism and cerebral hemorrhage; also in the insane, in infants and those suffering from laryngeal and deglutitive paralysis. Submersion may be followed by abscess or gangrene. Operations on the upper respiratory tract or face under general anesthesia are particularly apt to lead to the passage of infected material into the bronchi. The inhalation of foreign bodies, such as pins, tacks, tooth fragments and tobacco, if not removed, will usually result in suppuration or gangrenous lesions. Aspiration of infective material from putrid bronchitis or a bronchiectatic cavity is equally dangerous.

(4) INFECTED EMBOLI.—These are perhaps the most frequent cause of abscess or gangrene of the lung. An infective or suppurative process anywhere in the general venous circuit may result in the detachment of infected emboli and their lodgment in a pulmonary vessel, producing infarction and subsequent suppuration or putrefaction, according to the nature of the organisms present. Simple infarcts may possibly undergo infection from a purulent bronchitis. Puerperal sepsis, septic metritis or endometritis, septic thrombophlebitis, septic peritonitis and endocarditis, all occasionally give rise to septic emboli and abscess or gangrene. Suppurative middle ear disease, with septic thrombosis of the sigmoid sinus and internal jugular vein, is an occasional cause. Suppurative appendicitis, where the organ was retrocecal in its location, has been the cause in four of the author's cases. Abdominal operations and operations on hemorrhoids or varicose veins of the lower extremities are complicated by pulmonary embolus, and abscess or gangrene may develop.

(5) TRAUMA.—That perforating wounds of the chest should lead to infection and suppurative or putrefactive processes is readily realized. The mechanism of simple contusions or crushing injuries without puncture is, however, not so clear. Laceration of pulmonary parenchyma with infection from the bronchi affords the most plausible explanation.

(6) Extension from Neighboring Structures.—Extension of suppuration may occur from pleura to lungs. In these cases the primary suppurative focus is difficult of determination. Extension from putrid bronchitis or bronchiectasis occurs by aspiration. Abscess of the liver, particularly the amebic form, may rupture through the diaphragm into the lung, as may pus in the lesser peritoneal cavity. Abscess or gangrene of the lung rarely develops from mediastinal tumors, esophageal carcinoma, carious vertebræ, aortic aneurysm and carcinoma of the lung.

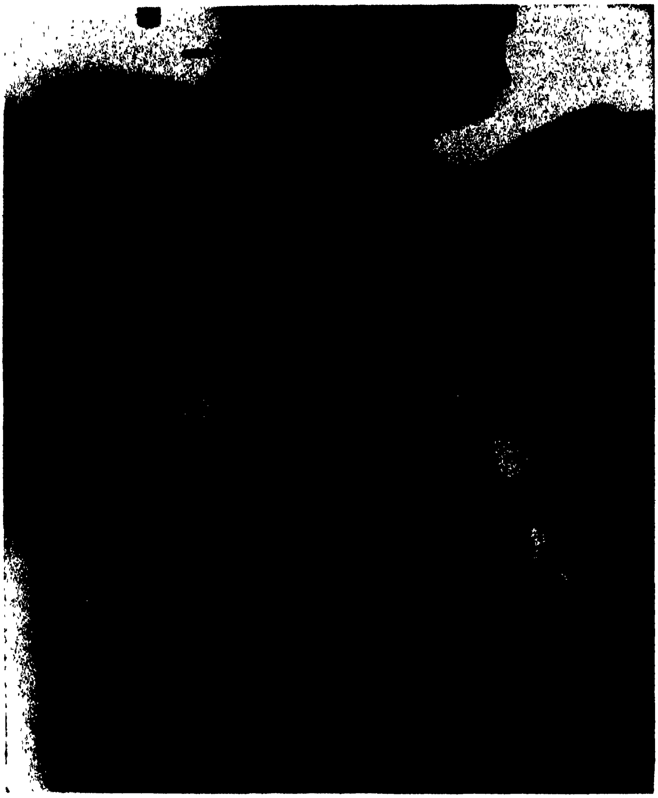

Fig. 7.—Chronic Abscess in Upper Lobe of Lung.

Symptomatology.—Clinical History.—Clinically, abscess differs from gangrene principally in degree, and a sharp distinction between them is impossible. An abscess may develop into a gangrene or vice versa, and the development of either condition depends rather upon the nature of the bacterial invasion than upon the degree of necrosis.

The symptoms are frequently disguised by the symptoms of the primary disorder. When the abscess or gangrene develops in the course of an acute pneumonia the usual crisis does not occur; the temperature persists and assumes a severe septic type, and the consolidated lung fails to undergo resolution. The cough is apt to become more severe and harassing, and the sputum changes from the rusty tenacious type to a mucopurulent and purulent kind. There may be chills, remittent or intermittent fever and profuse sweats, and the patient's condition becomes decidedly septic. Emaciation and prostration supervene and progress, until during some violent paroxysm of coughing, rupture of the abscess into a bronchus takes place. The amount of pus expectorated, when rupture occurs, varies with the size and location of the abscess. In some instances almost complete evacuation may occur at once, and a rapid convalescence be established. In others the purulent sputum continues, the drainage being incomplete, and chronic lung abscess results. Imperfect drainage frequently leads to periodic evacuation, influenced to a marked degree by the position of the patient. This seems to be more common in abscess of the lower lobes of the lung. The most striking symptom of lung abscess is the sudden expectoration of a large amount of pus containing elastic fibers, fragments of lung tissue and hematoidin crystals. When multiple foci of suppuration or putrefaction exist, even the expectoration of large quantities of purulent material may not appreciably alter the condition of the patient, and death occurs from sepsis.

Abscess or gangrene following bronchopneumonia, aspiration pneumonia, foreign bodies in the bronchi, or extension of the process from neighboring organs, present little that is characteristic. If they are of embolic origin, the symptoms depend upon the number of necrotic foci, and are particularly apt to be disguised by those of the general infection. Clinically, gangrene is distinguished from abscess by the evidence of putrefaction. The constitutional depression is more severe, the sputum is more often brownish or chocolate in color, is more offensive, and the relief from expectoration and evacuation is not as pronounced.

Special Symptoms.—*Fever.*—Abscess or gangrene usually complicates diseases already attended by fever; hence their development can result merely in a modification of the range or type of temperature. The temperature usually assumes a distinctly septic type with morning remissions and evening exacerbations. Chills and sweats more commonly accompany the fever in gangrene than in abscess. Their intensity varies with the nature and extent of the infection and the acuteness of the process. In chronic abscess even large quantities of pus may accumulate, and be expectorated daily without complaint of chills or sweats. After evacuation the temperature curve depends upon the freedom with which the abscess drains. If the drainage is good, the temperature soon reaches normal; if inadequate and intermittent, a mild septic temperature may persist for months. In gangrene the septic temperature often persists in spite of drainage; and where the putrefactive process is diffuse, septic symptoms prevail to the end.

Cough.—This is present in all cases, but varies greatly in intensity. Before communication with a bronchus is established there is nothing distinctive in the cough. It may be not unlike that in a pneumonia, a pleurisy, or simple bronchitis. When the abscess is single and of some size, a violent paroxysm of coughing usually accompanies the rupture into a bronchus; the cough thereafter is apt to be paroxysmal in type. In gangrene the cough is usually intense, even when unproductive. When the bronchial mucosa becomes bathed in the putrefactive material from the necrotic area, an intense bronchitis develops, and the cough becomes extremely distressing.

Expectoration.—In abscess before evacuation, the expectorated material may present little that is characteristic. In gangrene the offensive odor of the breath, even with scant expectoration, is very suggestive. When free communication with a bronchus has become established, the expectoration is the most characteristic symptom of both abscess and gangrene. In abscess the evacuation is frequently sudden, a large quantity of creamy, greenish or brownish material being expectorated. Examined microscopically, this is found to consist of pus-cells, epithelial cells, fragments of lung tissue, elastic fibers, hematoidin crystals and microörganisms. With effectual drainage, the expectoration gradually diminishes, and finally ceases entirely. With inefficient drainage, expectoration of pus may continue intermittently for a long time, and the material lose many of the characteristics of acute abscess. The odor of the evacuated material is, as a rule, inoffensive. It has been described as sweetish, stale, musty and fetid. Admixture of blood may give a brownish tinge to the sputum, or pure blood may be expectorated, although rarely in large amounts.

Pus from large and single abscesses is likely to be homogeneous, while that from multiple small abscesses is mixed with mucus. On standing the sputum may separate into layers, the lower one consisting of pus, the upper one of mucus, and the middle one of saliva.

Elastic tissue is found in the fragments of pulmonary tissue. Its presence is a certain indication of suppurative or necrotic lesions. It may be identified with the low power, as grayish-yellow spots, when the sputum is pressed between two glass slides, and examined over a black background. Under high power, it appears as refractive fibers or bundles of fibers with a wavy outline, and presenting an alveolar arrangement.

Hematoidin crystals appear as golden-brown plates and star-like forms. The expectoration in gangrene is distinguished by its extremely fetid odor and its color. The odor is often as distressing to the patient himself as it is to his attendants. It is said to be due to the presence of skatol, a decomposition product of animal proteins, and resembles that of fecal matter or putrefying flesh. It is extremely penetrating and permeates the surrounding atmosphere. The sputum is of a dirty grayish or brownish color. If collected in a glass, it soon separates into three layers. The bottom layer is thick, yellowish or greenish-brown, and consists of pus, pulmonary tissue fragments, elastic tissue and bacteria. Above this is a transparent stratum of serous fluid containing flocculi, while the top layer is a yellowish, frothy one. Dittrich's plugs may also be present in the lower stratum. They are yellowish-brown masses consisting of oil drops, crystals, and bacteria, and are said to be responsible for the disgusting odor of the sputum. Traube and Filehne have pointed out that in the sputum of gangrene, elastic tissue may be digested by a tryptogenic ferment and may therefore be absent.

Pain.—The amount of pain depends upon the degree of pleuritic involvement. In abscess or gangrene of embolic origin, pain is often the earliest manifestation of pulmonary mischief. In superficially located lesions, pain may be a prominent symptom until adhesion of the pleuritic surfaces has taken place.

Septic Symptoms.—The degree of pyrexia, anorexia, sweating, diarrhea and prostration varies, and is dependent upon the extent and nature of the process. As a rule, these symptoms are more pronounced in gangrene, in which the constitutional depression is frequently out of all proportion to the local physical findings. The pulse is usually rapid, soft and compressible, and indicative of the severity of the infection.

PHYSICAL FINDINGS.—The physical signs present nothing that is characteristic either of abscess or gangrene. In abscess, prior to evacuation, the physical signs are simply those of increased density or consolidation. After evacuation, if the abscess cavity is of considerable size, the signs of cavity are present. During the entire course of a gangrenous process, the physical examination may reveal nothing more than the evidence of consolidation and softening.

Inspection.—This gives us no information except such as points to some pulmonary involvement. When in the course of an appendicitis, puerperal sepsis, phlebitis or liver abscess, rapid and restricted breathing and pain on one side occur, they are suggestive of pulmonary embolus and abscess or gangrene may be expected to develop.

Palpation.—Palpation confirms inspection regarding any restriction in respiratory movement. Over lesions of considerable size, and such as are superficially located, alteration of vocal fremitus may be detected. This may consist in diminution or exaggeration, depending upon the stage of the process, and the degree of pneumonic infiltration around it.

Percussion.—Dullness on percussion is found in most cases; it is due largely to infiltration of the neighboring lung. After evacuation, a tympanitic note may be elicited from the center of an area of dullness. Cracked-pot resonance or a change in the percussion note after profuse expectoration, change of position, etc., are occasionally demonstrable; they are valuable signs of cavity.

Auscultation.—Before communication with a bronchus is established, the breath sounds are identical with those found over consolidated lung areas from any cause. Liquefaction of the necrotic focus may lead to diminution of breath sounds, vocal and whispered fremitus, and the appearance of numerous moist râles over this and the surrounding regions. After evacuation, the breath sounds again become distinctly bronchial or may be cavernous. Large bubbling râles or fine metallic râles are abundant; the whisper and voice sounds are metallic or amphoric in quality. Multiple necrotic foci frequently give rise to no other auscultatory signs than those of consolidation and moisture.

LABORATORY FINDINGS.—Careful and diligent microscopic search of the expectorated material for fragments of the lung tissue, elastic fibers and tubercle bacilli should be made in all cases of delayed resolution, and where pulmonary complications develop during the course of some general or localized infectious process. The discovery of elastic tissue is frequently the earliest and most positive confirmation of the presence of a suspected necrotic lesion.

X-ray examination, both fluoroscopic and roentgenographic, should be resorted to in all cases for the purpose of determining the site and number of lesions as well as the presence of foreign bodies in the bronchi or lung tissue.

Diagnosis.—This can be positively made only upon data furnished by the character and content of the expectorated material. Careful examination into the previous history is of great importance. A recent lobar or bronchopneumonia with delayed or incomplete resolution should always arouse a suspicion of abscess or gangrene, particularly when the temperature and other symptoms point to sepsis. Pulmonary consolidation with cough and pleuritic pain following the inhalation of a foreign body, etherization, operation on the nose or throat, thoracic trauma, abdominal, pelvic or rectal operation, puerperal and other septic conditions and abscess of the liver are decidedly suggestive of an infected necrotic process. A circumscribed shadow or shadows found upon *x*-ray examination and complicating any septic condition are of aid in diagnosis. Cough and pleuritic pain are almost constant. Extreme fetor of the breath may at times enable one to diagnose gangrene, even before any amount of expectoration occurs. In the large majority of cases, however, a certain diagnosis is impossible until the characteristic elastic fibers are found in the sputum. The only physical signs of value in the diagnosis of abscess or gangrene are the signs of cavity.

The *differential diagnosis* between abscess and *gangrene* is not always easy. The sudden expectoration of a large amount of purulent material not highly offensive points to abscess, particularly if signs of cavity can be elicited by physical examination after evacuation. The expectoration of small amounts of reddish or brownish extremely fetid sputum indicates gangrene. In general septic manifestations and prostration are more marked in gangrene than in abscess. It should not be forgotten that an abscess cavity, even a tuberculous one, may become the seat of a gangrenous process.

The differentiation between chronic lung abscess and *bronchiectasis* is often impossible, particularly when the conditions are associated. The expectoration in both may be devoid of elastic tissue or contain it. The history of bronchiectasis is one of gradual development without septic manifestations, and the manner of evacuation differs. The location of the lesion in a lower lobe, particularly if on the right side, favors abscess. Hypertrophic pulmonary osteo-arthropathy may occur in chronic lung abscess as well as in bronchiectasis, pulmonary tuberculosis and chronic emphysema (D. B. Phemister). Pulmonary abscess may be closely simulated by ruptured, encysted and interlobar empyema. In the differential diagnosis, a careful inquiry into the preceding or associated infection is important. When rupture of an empyema has taken place the signs of pneumothorax supervene. Elastic tissue may be found in the pus from a ruptured empyema. Its presence, therefore, does not exclude this affection. Early signs and symptoms of pleurisy are usually more pronounced in empyema than in abscess or gangrene. In the differential diagnosis of interlobar and diaphragmatic empyema from abscess or gangrene, the *x*-ray is of decided value.

Amebic abscess of the liver which has ruptured into the lung and a bronchus can be recognized by: (*a*) the history of amebic infection; (*b*) previous symptoms of liver involvement; (*c*) the presence of *Ameba histolytica* in the sputum.

Fetid bronchitis and *bronchorrhea* are distinguished from abscess or gangrene by the absence of elastic tissue and hematoidin crystals and by the absence of signs of cavity upon physical and *x*-ray examination.

In abscess or gangrene with a history of previous symptoms indicative of pulmonary involvement, *tuberculosis* must always be excluded. Exposure to tuberculous infection, gradual loss of weight and strength, early hemoptysis, afternoon temperature and night sweats prior to the development of abscess or gangrene indicate tuberculosis. Careful and repeated examinations of the sputum for tubercle bacilli, preferably by the antiformin method, should be made in all such cases. Tuberculous abscesses are more often located at the apices, and non-tuberculous abscesses in the lower lobes. Lord, however, reports four cases of abscess in the superior lobes, found at autopsy, without gross or microscopic evidence of tuberculosis. Where a definite history of previous tuberculosis is wanting, the detection of the tubercle bacillus in the sputum is the only positive means of diagnosis. Whenever abscess or gangrene of the lung is suspected, the sputum should in addition be examined for actinomyces and yeast fungi. If the process is gangrenous from the beginning, the question of tuberculosis can as a rule be disregarded.

Exploratory puncture, although a well-recognized and frequent procedure, is, in the author's experience, seldom justifiable as a means of diagnosis of abscess or gangrene. No harm may result if the area can be accurately outlined by physical examination and pleural surfaces are adherent. If, however, the abscess is deeply situated and pleural surfaces not adherent, serious consequences may follow. He has found a much safer procedure in all cases to be exposure by thoracostomy, although there is some difference of opinion as to the advisability of this procedure. If the pleural surfaces are found to be adherent, the exploratory needle may be used without danger. If not, the parietal should be sutured to the costal pleura, before exploratory puncture of the lung is made.

Complications.—A pleuritic involvement almost always accompanies abscess or gangrene of the lung. If the lesion is fairly deep seated, a fibrinous exudate with firm adhesions of pleural surfaces develops. Superficial necrotic lesions frequently give rise to purulent exudation, and, if the abscess or gangrenous process breaks through the visceral pleura, to pyopneumothorax. Purulent and putrid pleurisies are more common in gangrene. Purulent pericarditis may also occur. Pneumonic infiltration of the neighboring lung tissue is constant; it may extend to a considerable distance from the necrotic area. Bronchopneumonia and aspiration pneumonia will multiply abscesses, and gangrenous areas may develop from aspiration of purulent material.

Hemoptysis is more serious and frequent in gangrene than abscess. Fatal hemorrhages have been reported in both. Severe hemorrhage is more often a late occurrence and proceeds from a vessel in the wall or free in the lumen of the cavity. Of 50 cases of gangrene at the Massachusetts General Hospital, one died from hemorrhage (Lord).

Metastatic cerebral abscesses occur. They are the result of septic emboli which usually lodge in the cortical distribution of the middle cerebral artery; they give rise to monoplegias, hemiplegia or attacks of jacksonian epilepsy. Metastatic abscesses in the liver, spleen and kidneys also occur.

Hypertrophic, pulmonary osteo-arthropathy occurs in chronic pulmonary abscess. Amyloid disease may also develop.

Treatment.—This is medical and surgical. The medical treatment is expectant and supportive, and is indicated during the period of uncertainty as to the location, size and character of the lesions. Abscesses of the lung frequently heal spontaneously by rupture and drainage through a bronchus: hence, if the patient's general condition permits, expectant treatment is justifiable, for it may in some instances afford the patient the better chance for recovery. If rupture does not occur, a period of from two to four weeks is usually sufficient to insure firm pleuritic adhesions, and make operative procedure safe and comparatively simple.

The aim of all medical treatment is to conserve the patient's strength and to build up a resistance against the infection. Absolute rest in bed is of prime importance. The **sick room** should be large, well lighted and ventilated. The **diet** should be light, nutritious and abundant. If digestion is not seriously disturbed, extra feedings between regular meal times are advised. The **sputum** should be received in a special receptacle which can be burned; the patient should be warned against swallowing his sputum. If after rupture it is found that a certain position favors the evacuation of the abscess, this position should be assumed at least once or twice daily. General and cardiac tonics such as **strychnin, caffein, digitalis, iron** and **arsenic** may be administered as special indication arises. **Rest, pure air and nourishment** are the only rational means at present available for combating these infections. Remedies such as **creosote, guaiacol, digitalis and cod-liver oil,** that are apt to disturb appetite and digestion, should therefore be administered with caution. The giving of expectorants should be avoided for the same reason.

Inhalations of oleum terebinthinæ, creosote or **carbolic acid** have been highly recommended by some authors, particularly in the treatment of gangrene.

Oil of turpentine, oil of eucalyptus and myrtol are valuable as deodorants.

Narcotics such as **morphin, codein or heroin** should be used only when a dry and irritating cough interferes with a proper amount of rest and sleep.

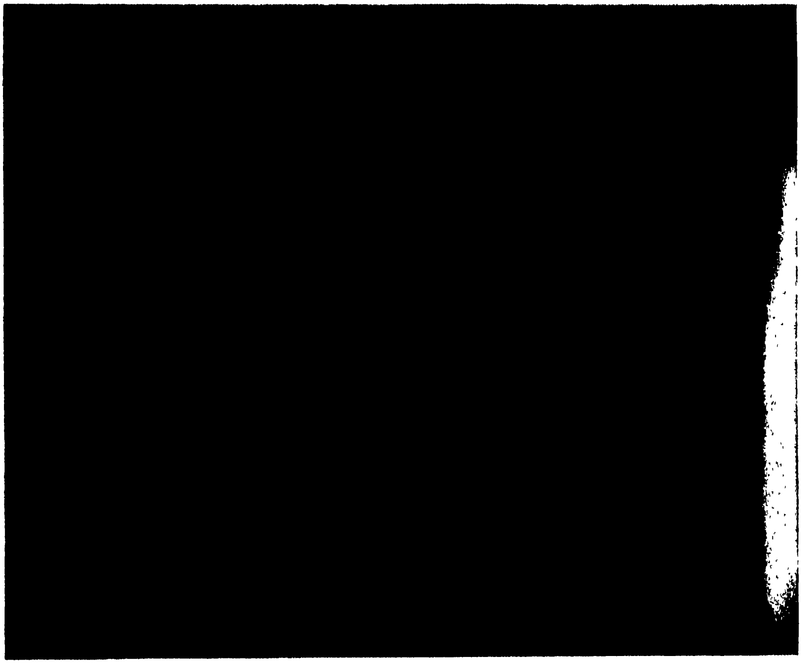

Fig. 8.—Extensive Gangrenous Process Engrafted upon a Chronic Tuberculosis of the Lung.

In general, it may be said that the *expectant plan* of treatment is more safely carried out in abscess than in gangrene.

The treatment of an abscess subsequent to rupture and evacuation is determined by the efficiency of the drainage and the degree of improvement which follows. As soon as it is evident that the abscess does not drain properly and cannot heal, *surgical interference* should be advised. In gangrene little improvement may follow even copious expectoration, and operative procedure should not be delayed.

Multiple areas of abscess or gangrene are often best treated by the *expectant plan,* although even these have been successfully attacked by the surgeon. Statistics collected by Garre and Sultan, and Kissling, indicate that the mortality following surgical treatment is considerably less than that experienced under medical management. This is particularly true of gangrenous processes. Exact and definite localization of the lesion by means of the *x*-ray and modern surgical technic are doing much to remove the management of abscess and gangrene from the domain of internal medicine to that of surgery, where it rightly belongs. The ideal treatment of these lesions, wherever situated, is early and free **drainage.** Recovery under this treatment is not only most prompt and certain, but chronic abscesses and other serious pulmonary lesions and complications are prevented.

In acute cases where the lesion has been definitely located, **thoracostomy** should be performed. If the pleural surfaces are found adherent, the abscess can, as a rule, be reached without much difficulty and good drainage secured. If no adhesions exist, the parietal should be stitched to the costal pleura, the wound packed, and incision of the pleura and exploration of the lung postponed until firm adhesions have occurred.

In chronic lung abscess or gangrene, **pneumotomy** or extensive **resection of the ribs** with collapse of the lung are the surgical procedures commonly recommended. Resection of a lobe of the lung for abscess has been successfully performed. Artificial pneumothorax has also been employed in the treatment of abscess, both acute and chronic. Its usefulness in the latter is, however, limited, because of the presence of extensive adhesions.

Prognosis.—The mortality of abscess and gangrene under expectant management is said by Lenhartz to be in the neighborhood of 70 per cent. Garre collected 182 cases of abscess and 281 cases of gangrene which were operated upon with a mortality of 18.5 and 29.3 per cent. respectively. The operative mortality is greater in chronic than in acute cases. The prognosis is always grave, especially in gangrene; the importance of the factors influencing the outcome is difficult to estimate. In abscess or gangrene following croupous pneumonia or trauma, the prognosis is more favorable than that following bronchopneumonia, foreign bodies in the bronchi or septic emboli. Nevertheless, the author has witnessed spontaneous recovery in 5 cases of metastatic lung abscess, 3 of which followed suppurative appendicitis and 2 puerperal infection. Complete recovery occurs in both affections by rupture and drainage into a bronchus. Multiple abscesses or gangrenous lesions are nearly always fatal. Upper lobe lesions as a rule drain better than lower; hence the prognosis is better. Recovery is not always complete: chronic lung abscess, bronchiectasis and interstitial pneumonia may result. Complications such as hemorrhage, cerebral abscess and pyopneumothorax are serious. Persistence of septic symptoms after rupture or drainage indicates a multiplicity of lesions or extension of the necrotic process and an unfavorable prognosis. Early *x*-ray localization and skilled surgical intervention offers the best prognosis in both abscess and gangrene.

Pathology.—The gross appearance varies considerably. Pulmonary abscesses appear as grayish or yellowish areas from which pus exudes, or may be expressed. Gangrenous areas are darker, greenish or reddish-brown. Either lesions may be single or multiple and may vary greatly in size. An abscess or a gangrenous area can be readily distinguished from areas of gray or red hepatization by its softness and the ease with which the pulmonary tissue can be broken down. In gangrene the putrid odor is readily perceived. The wall of the necrotic area may be a well-defined, dense connective tissue barrier, or the disease area may merge almost imperceptibly into the healthy tissue. The older and more quiescent the process, the more definite the limiting wall. Superficially situated lesions are readily located by fibrinous or purulent exudates on the pleural surfaces. The abscess cavity is surrounded by an area of hepatization and edema varying with age and progressiveness of the infection. The bronchi leading from the affected area show intense inflammation. If the contents of the abscess cavity are freely evacuated, cicatrization and healing may occur. Pyopneumothorax may be present. In abscess or gangrene the result of septic emboli, the lesion is apt to be wedge-shaped, corresponding to the area supplied by the plugged vessel.

Microscopically the disease focus consists of pulmonary elastic tissue, pus-cells, blood, detritus and bacteria. The wall of the abscess cavity is infiltrated with leukocytes and proliferated, connective tissue cells. The surrounding tissue shows cellular infiltration and edema. A gangrenous area is usually sharply differentiated from the surrounding lung tissue by a zone of intense hyperemia, but even in gangrene a pyogenic membrane may occasionally be formed. In chronic abscess or gangrene this membrane continues to secrete pus and interferes with collapse and healing of the cavity. The greater part of a lobe of the lung may be the seat of a diffuse gangrenous process and the lung tissue converted into a soft pulpy malodorous mass without definite boundaries. This type is said to be the result of inhalation of septic material. Metastatic abscesses in the brain, spleen, liver, kidneys and other organs are commonly found. Abscess or gangrenous processes occur most commonly in the lower lobes, especially the right, and in close proximity to the pleural surface. Of 30 cases examined postmortem at the Massachusetts General Hospital, in 28 the lesion was just beneath the pleura or extended into it (Lord). Metastatic pulmonary abscesses usually occur in the lower lobe of the right lung. The five metastatic abscesses previously referred to were all located in the above-named region. Abscess or gangrene following bronchopneumonia, aspiration pneumonia and metastatic abscesses are more apt to be multiple. Chronic abscess is likely to become multiple by extension or by aspiration of infected material into other parts.

TUMORS OF THE LUNG

Etiology.—The etiology of benign and primary malignant tumors of the lung is still clouded in mystery. Sarcoma of the lung, like sarcoma elsewhere, is more common before middle age, while carcinoma occurs later in life. Primary carcinomata of the lung are said to occur more often in males, and secondary ones in females. Trauma has been cited by many observers as a cause of malignant growths of the lungs. Local irritation from inhalation of dust such as the cobalt miners are subjected to is said to predispose to malignant disease. Pulmonary malignancy and tuberculosis are frequently associated. The right lung appears to be more often the seat of primary tumor.

Primary carcinoma of the lungs and pleura is considered relatively rare. Primary sarcoma is even less frequent. Secondary invasion of the lung by malignant growths occurs by direct extension or by metastases. The primary growth may be in the stomach, liver, pancreas, prostate, bones or mammary gland. Hypernephromata and malignant deciduomata frequently metastasize to the lungs. Malignant deciduoma involves the lungs in about 50 per cent. of cases (Morris and Landis).

Symptomatology.—Clinical History.—The symptoms vary with the location and size of the tumor, and are influenced but little by its nature, whether sarcomatous or carcinomatous, primary or secondary.

Cough.—This is usually an early and constant symptom, but may be absent in rare instances. It is unproductive, often paroxysmal and distressing. Large tumors in close proximity to the trachea or a large bronchus, or marked pleural involvement, aggravate this symptom.

Expectoration.—This is rarely profuse, consisting of small amounts of mucous or mucopurulent material. The sputum may be dark red or brownish from admixture with blood. Profuse hemoptysis is rare. Shreds or fragments of carcinomatous or sarcomatous tissue are occasionally found in the sputum.

Pain.—The pain varies with the amount of pressure exerted by the tumor, and the degree of pleural involvement. It is a most constant symptom, and may be complained of long before other evidence of disease in the lungs becomes manifest. Pressure pain from tumor is constant and boring in character, often radiating to the shoulders and arms, resembling the pain in aortic aneurysm. In other cases the pain is entirely intercostal; the diagnosis of intercostal neuralgia is the one primarily made. Involvement of the pleura either through pleuritis or tumor cell invasion leads to severe pain.

Pressure Symptoms.—These are most prominent in primary neoplasms occupying the lung hila or the upper regions. Pressure upon large venous trunks in the anterior mediastinum, particularly the vena cava superior and inferior or one of their large branches, leads to dilatation of the superficial veins of the neck, chest and abdomen. The growth may compress the esophagus and recurrent laryngeal nerve, producing dysphagia, dysphonia and aphonia. Pressure on the ciliospinal branch of the sympathetic leads to pupillary inequality. Extension of the growth to the vertebral column and cord may by encroachment or direct invasion produce pressure myelitis.

Dyspnea.—This is a usual and early symptom, varying with the degree of pressure upon large bronchi, pleural or mediastinal involvement. Lymphosarcoma of the mediastinum or extensive involvement of this region by Hodgkin's disease often leads to violent dyspnea. Cyanosis may be present, and in advanced cases may become extreme.

General Symptoms.—Cerebral symptoms, the result of tumor metastases, may develop. Fever of an irregular, intermittent type is common, especially in the later stages. Chills and sweats are uncommon.

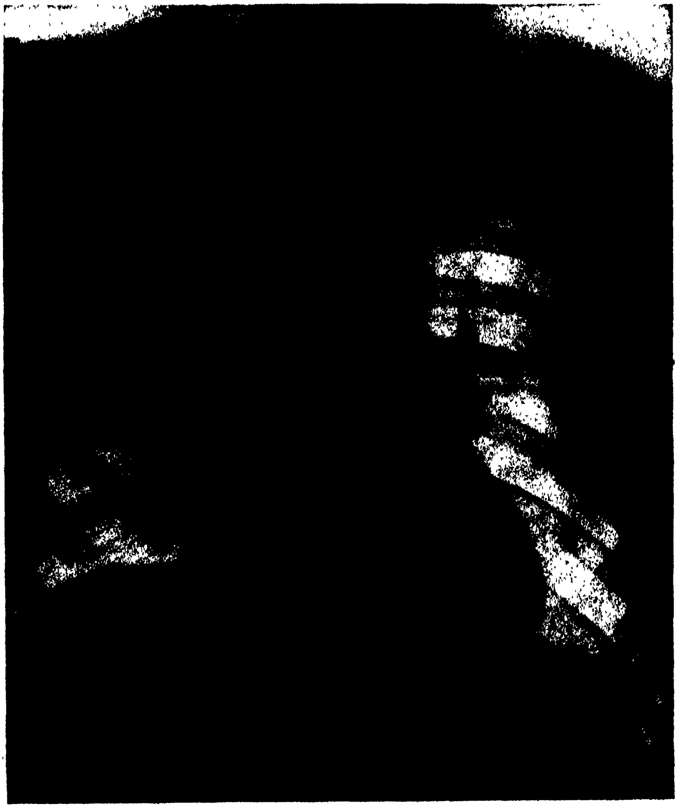

Fig. 9.—Benign Tumor of the Lung of Thirty-Five Years' Standing.

Loss of weight and strength, anemia, cachexia and emaciation occur as the disease advances, probably as much the result of cough, dyspnea and insomnia as from absorption of toxic material.

Physical Findings.—*Inspection* of the thorax reveals modification of the normal outline, such as localized bulging or a general enlargement of one side. Occlusion of a large bronchus by the growth may, however, lead to collapse and retraction of the lung and to an actual diminution in the size of the affected side. Restricted respiratory movement is an early and constant sign. Dilatation of the superficial veins of the chest, especially the upper part, is common. Enlargement of the superficial veins may also be noticeable in the arms, lower thorax and upper abdomen. In addition, venous stasis is manifested by cyanosis of the face and neck and by edema of the face, neck and chest. If the tumor is in contact with the aorta, the pulsations of the latter may be transmitted and be visible. Cardiac displacement is frequently seen. Clubbing of the finger ends (hypertrophic pulmonary osteo-arthropathy) develops with great rapidity in some cases. Direct inspection of the tumor may be possible through the bronchoscope.

Palpation.—This confirms inspection as to restriction of respiratory movement, pulsation of mass, and cardiac displacement. The pulsation, however, is not of the expansile type felt in aneurysm. A tumor in close proximity to both aorta and trachea may give rise to a distinct tracheal tug. Tactile fremitus, voice and whispered sounds are usually diminished or absent over the growth. Tender areas can frequently be found on pressure. Palpation also reveals enlarged lymph-glands in the cervical and axillary regions, and inequality of the radial pulses.

Percussion.—The findings upon percussion vary with the size and location of the growth and the presence or absence of pleural effusion. Small and deeply seated tumor masses may give rise to no appreciable impairment of pulmonary resonance. Large primary tumors which have their origin in a large bronchus give rise to dullness, or flatness in the sternal, infraclavicular, and interscapular regions. Especially striking is the sense of resistance to the percussing finger which one experiences in such examinations. A remarkable transition from tympany to dullness and again from dullness to tympany has been observed by Fraenkel and Greenwald (Babcock).

Auscultation.—Breath sounds vary with conditions present. If the growth is limited to the root of the lung or mediastinum, the breath sounds may not be altered. Partial occlusion of a large bronchus may produce a loud, stridulous sound. Complete obstruction of a bronchus with pulmonary atelectasis causes a disappearance of all breath sounds over the affected area. Murmurs due to compression of large venous trunks are occasionally heard. An associated bronchitis or a disintegration of a tumor mass may give rise to moist râles. Effusion into the pleural cavity causes a disappearance of all breath sounds. Extensive infiltration with small tumor masses gives rise to bronchial breathing.

SPECIAL EXAMINATIONS.—*Sputum.*—Microscopically the sputum presents nothing characteristic. It is seldom profuse, usually mucoid, mucopurulent or blood-stained. Slight hemoptysis is said to occur in from one-third to one-half of all cases of malignant neoplasm. Profuse and even fatal hemorrhage has occurred. Tumor fragments in the form of grayish or pinkish particles or shreds are occasionally found in the sputum. Stained and examined microscopically, these fragments are seen to consist of groups or clusters of cells highly suggestive of malignant disease. Sputum composed largely of polymorphous, polygonal, unpigmented cells with well-defined nuclei, is said by Hampeln to be characteristic of malignant growth in the lung. Lenhartz attaches much importance to strongly refractive spherical bodies containing fat granules which he found in the sputum.

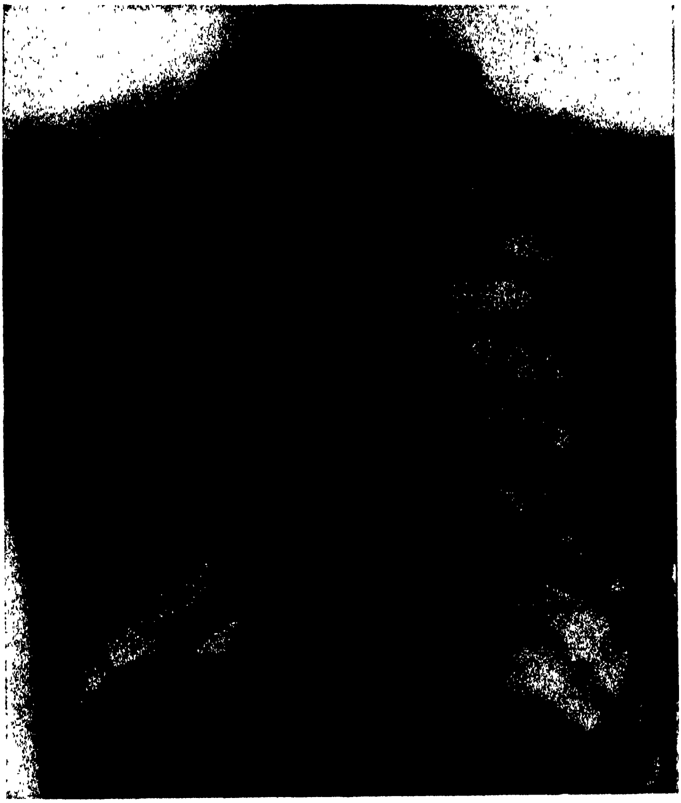

FIG. 10. METASTATIC SARCOMA OF THE LUNG WHICH DEVELOPED FIVE YEARS AFTER AMPUTATION OF A LEG.

Pleuritic Exudate.—Pleuritic fluid in malignant disease of the lung in the large majority of instances is of the hemorrhagic type. An abundance of spindle-cells and cells showing mitotic figures are suggestive of new growth. Small shreds of tissue removed with the exploring trochar may contain sarcoma or carcinoma cells.

X-ray.—This has become an indispensable aid in the examination and diagnosis of tumors of the thoracic cavity. The location and size of the new growth can almost always be determined with considerable accuracy. McMahon and Carman state that a definite diagnosis of primary carcinoma of the lung is possible in all except the very early and atypical cases by roentgen examination. They have furthermore determined that by this means the infiltrative, miliary, and mixed types of carcinoma can be differentiated from each other, and from inflammatory changes and other primary or secondary neoplasms.

Bronchoscopy.—Demonstration of the tumors in the bronchi by means of the bronchoscope is possible. The use of this instrument, however, is limited to the hands of the expert.

Exploratory Puncture.—This is rarely justifiable except for the purpose of determining the nature of the pleuritic effusion. If an early positive diagnosis is desired, exploratory thoracotomy with removal of a section of the growth is the safer procedure.

Diagnosis.—The diagnosis of primary neoplasms of the lung is still difficult, even though much simplified by modern roentgenographic means. Severe pain, constant or paroxysmal, with a tendency to increase rather than abate, is an important symptom of new growth. Circumscribed or unilateral prominence of the chest wall with definite evidence of pressure upon large venous trunks and other mediastinal structures in a patient suffering from cough, dyspnea and localized cyanosis is reliable evidence of tumor of the lung. Diminution or absence of breath sounds, vocal resonance, tactile fremitus, and the absence of expansile pulsation and bruit over the consolidated, bulging area are important findings, from the standpoint of differential diagnosis. If in addition a hemorrhagic effusion is found in the pleural cavity, the diagnosis of tumor may be considered justifiable.

The roentgen findings in primary carcinoma of the lung are said by McMahon and Carman to be quite typical and pathognomonic. A careful correlation of the roentgen findings, the clinical history, the physical and laboratory findings, is, however, urged by these authors. Positive diagnosis as to the nature of the primary growth rests upon the detection of characteristic tumor shreds or cells in the sputum and pleuritic exudate, and the examination of tumor tissue removed by thoracotomy or by resection of a neighboring infiltrated gland.

The diagnosis of secondary neoplasms is less difficult, providing a reliable history is obtainable. Pulmonary lesions developing in an individual previously operated upon for carcinoma of the breast, stomach, uterus, skin or bone, or in those in whom carcinoma or sarcoma is present at the time, point strongly to secondary metastatic invasion.

DIFFERENTIAL DIAGNOSIS.—*Pulmonary Tuberculosis.*—Severe pain and pressure effects are usually absent. The temperature is usually higher and more likely to be of the intermittent type. There is flattening of the chest over the area involved rather than bulging, and the lesion is much more apt to be found in one or both apices. The physical findings over the consolidated area correspond to those usually found: viz., bronchial or bronchovesicular breathing, increase of vocal and tactile fremitus and râles. Expectoration is generally much more profuse, and the finding of tubercle bacilli definitely settles the diagnosis. *X*-ray examination shows the lesions more circumscribed, located peripherally in the apices, and cavities present.

Aortic Aneurysm.—The differentiation of new growth from aortic aneurysm frequently offers considerable difficulty, inasmuch as all the symptoms and signs of the former may also be present in the latter. The history of syphilitic infection, expansile pulsation of the tumor and aneurysmal bruit serve to distinguish one from the other. Roentgen examination reveals a pulsating tumor located in the upper thoracic region and springing from the aortic arch rather than from the roots of the lungs. Unequal and delayed pulsation in the radials is more frequent in aneurysm than in neoplasms.

Bronchiectatic Cavities and Chronic Abscess of the Lung.—These are distinguished by the history, the profuse purulent expectoration and the manner of evacuation of the cavity. Moore has shown that in bronchiectasis the roentgen shadow is fan-shaped and extends to the periphery. In chronic lung abscess, the area of density is circumscribed and there is evidence of cavitation.

Hodgkin's Disease.—In the early stages of a new growth a differentiation from Hodgkin's disease may not be an easy task. Involvement of cervical and axillary glands is earlier and more extensive. The tumor masses are usually limited to the mediastinum. Careful differential blood-count and microscopic examination of resected gland confirm the diagnosis.

Pleurisy with Effusion.—New growths may have their origin in the pleura as well as in the lung. In simple and tuberculous pleurisies the effusion is usually serous, while in neoplasm it is hemorrhagic. Enormously thickened pleuræ found upon exploratory puncture or *x*-ray examination indicate neoplasm. The roentgen shadow in effusion is dense and homogeneous, is located at the base of the thoracic cavity, and there is obliteration of the costophrenic angle.

Clinical Varieties.—Tumors of the lung may be classed as benign and malignant. Malignant tumors may be primary or secondary. Benign tumors are fibroma, fibromyoma, osteoma, lipoma, and dermoid cysts.

Primary malignant tumors are carcinoma and sarcoma. Secondary metastatic tumors are carcinoma, sarcoma, hypernephroma, and malignant deciduoma. Primary carcinoma of the lung may further be divided into the infiltrative, the miliary and the mixed types. Sarcomata are round-cell sarcoma, spindle-cell sarcoma, giant-celled sarcoma, lymphosarcoma, myxosarcoma, and fibrosarcoma.

Treatment.—This is palliative and surgical. In the large majority of primary lung tumors a positive diagnosis is impossible, at a time when surgical treatment could be successfully instituted; hence palliative treatment is our only recourse. This consists in relieving the patient of pain, dyspnea, cough and insomnia. **Opium** and its derivatives, **morphin, codein,** or **heroin,** are indicated, and in the case of malignant rapidly growing tumor should be employed in doses sufficient to give the desired relief. **Strapping of the chest** may relieve pleuritic pain. The removal of pleuritic fluid may temporarily relieve dyspnea and pressure symptoms. **Surgical removal** of malignant tumors of the lung has been attempted in rare instances. Tschekan collected 12 cases, one-half of which died twenty-four hours after operation; the other half recovered. *X*-ray treatment has been followed by temporary improvement in some cases.

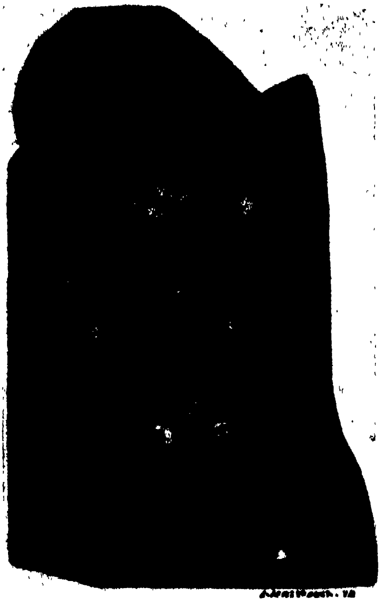

Fig. 11.—Gross Drawing of Carcinomatous Nodule in Lung, Primary in Mammary Gland. (McJunkin.)

Prognosis.—The prognosis in malignant neoplasms of the lung, either primary or secondary, is decidedly unfavorable. Death occurs in the majority of instances within a year. Benign tumors may exist for a lifetime without serious symptoms. The writer has personal knowledge of a benign tumor of the lung of considerable size which has existed for a period of thirty-five years, without producing other than slight pressure symptoms.

Pathology.—*Benign tumors* of the lungs are rare and are mostly of connective tissue origin. They rarely give rise to much disturbance and are frequently not discovered during life. *Osteomata, chondromata, fibromata* and *lipomata* are usually small and multiple. Calcified tuberculous lesions have been mistaken for osteomata.

Dermoid cysts are most commonly situated in the mediastinum, behind the upper part of the sternum. In this location they may give rise to cough, expectoration, pain and pressure symptoms. Infection of the cyst may occur and abscess develop. The cyst may rupture into a bronchus or through the chest wall. If the former, hair or teeth may be expectorated. If the latter, a permanent fistulous tract may remain. They appear before middle life and are of slower growth. A local fluctuating tumor over the sternum suggests dermoid cyst. *Adenomata* originating in the bronchial and mediastinal glands have been found.

Primary malignant tumor of the lung is rather infrequent. Lord states that in the combined statistics of Reinhard, Fuchs, Wolf, Passler and Froelich primary cancer was found but 105 times in 46,169 autopsies. McMahon and Carman have found the total authentic cases of primary carcinoma reported up to this time to be 428. They report upon 7 cases collected in the Mayo clinic. Tumors involving the bronchi or lung tissue by infiltration are usually malignant in type. *Primary sarcomata* are even less common; they occur as soft whitish or grayish, single or multiple, tumors. Extensive infiltration of pulmonary tissue and metastases are less frequent than in carcinoma. Many primary sarcomata of the lung have their origin in the mesothelium of the pleura. Histologically the small round-cell type is the most common.

Primary carcinomata nearly always originate in the columnar epithelial cells lining the bronchi. The growth often appears as a single rounded tumor mass projecting into a bronchus. Infiltration of neighboring bronchi, lung tissue and glandular structures occurs by direct extension. Less frequently the lung may be studded with small tumor masses resembling tubercles or both, the infiltrative type originating and extending along the bronchial tree, and the miliary type possibly being present in the same lung (mixed type). The growths are white, grayish or yellowish in color, rather hard when located in the bronchi, and softer, marrow-like, when found in the lung tissue. Cavitation may result from extrusion of the softened necrotic tissue into a bronchus. At times the growths may be found to be entirely subpleural.

The *bronchial lymph-glands* usually show *metastases*, the cervical and axillary less frequently. Metastases in the brain are quite common. They may also occur in the liver, spleen, kidneys, adrenals, bone and skin. Extensive infiltration of both lungs with carcinoma has been reported without metastases. Adjacent lung tissue may show emphysema, atelectasis, bronchopneumonia, interstitial pneumonia, abscess or gangrene. Tuberculosis and malignant disease of the lungs rarely coëxist. Pleural effusions of the hemorrhagic type are common. Malignant disease in the form of an endothelioma may originate in the pleura, and lead to great thickening of this membrane; or malignant disease may extend to this structure from the lung, producing extensive infiltration and adhesions. Pneumothorax has been observed. Direct invasion of the esophagus, trachea, pericardium and spinal canal has occurred.

Microscopically the appearance is quite constant and suggestive of bronchial origin. The prevailing type of cell is columnar or tubular. Flat-celled epithelial cancer is less common. Tubular carcinoma cells devoid of stroma are said to predominate in the nodular miliary type of the disease, while in the dense infiltrative type, there is much fibrous tissue without tubular arrangement. Cellular invasion of the smaller bronchi and alveoli is apparent. Areas of necrosis and cavitation may be observed microscopically. Carcinoma of the lung spreads by direct extension along the bronchi to the alveoli, by the lymphatic channels, and perhaps by aspiration of tumor particles, to areas quite distant from the original growth. Lymphosarcoma usually originates in the mediastinal lymph-glands, and there may be little actual invasion of lung tissue. Unilateral carcinoma with extensive pleural involvement occurs where there is direct extension from the neck, breast, mediastinum or abdomen. The interval between the appearance or removal of a primary malignant growth and its metastases in the lung may be one of years. The primary tumor is most commonly located in the esophagus, stomach, breast, liver, peritoneum, bowel, bones or testes. Pulmonary congestion, atelectasis, bronchopneumonia, abscess or gangrene occur; they are all secondary changes.

Secondary malignant disease of the lungs occurs with greater frequency than the primary. It is more often bilateral. It may occur by direct extension from neighboring organs or tissues or by metastases by way of the lymph or blood-vessels. The histology of the secondary tumors is usually that of the parent growth, although Lord states that metastatic lung tumors from osteosarcoma or chondrosarcoma may contain neither bone nor cartilage.

BIBLIOGRAPHY

ACHARD AND ROUILLARD. Gangrène pulmonaire consécutive à une contusion thoracique. Bull. et mém. Soc. de méd. d. hôp. de Paris, 1914, xxxvii, 1172-1175.

ADLER. Primary malignant growths of the lung and bronchi. New York, 1912.

ARMBRUSTER. Physiologische Studien über Lungenemphysem. Aerztl. Rundschau, München, 1915, xxv, 81-83.

ASCHOFF. Pathologische Anatomie. Jena, 1913.

AUER AND GATES. Experiments on the causation and amelioration of adrenalin pulmonary edema. Jour. Exper. Med., xxvi, No. II.

AUFRECHT. Diseases of bronchi, lungs and pleura. Nothnagel's Encyclopedia, 1902, p. 760.

BABCOCK. Diseases of the lungs, 1907, p. 693.

BASTEDO. The treatment of pulmonary edema in pneumonia. Jour. Am. Med. Assn., 1917, lxix, 800.

BIRCH-HIRSCHFELD. Deutsch. Arch. f. klin. Med., 1899, lxiv.

BOGHEAN. Berl. klin. Wchnschr., 1914, p. 1101.

BRUNS. Ztschr. f. exper. Path. u. Therap., 1910, vii, 494.

CHANARD. Le sarcome primitiv du poumon. 1914, xi, 1097-99.

CUNNINGHAM. Pub. 224. Carnegie Inst., Washington.

FRAENKEL. Deutsch. med. Wchnschr., 1903, p. 204.

——— Spezielle Pathologie und Therapie der Lungenkrankheiten. Berlin, 1904.

FRANK. Lung abscess as a sequel to tonsillectomy. Laryngoscope, 1917, xxvii, 474.

FREUND. Berl. klin. Wchnschr., 1912, xlix, 1695-99.

GARRÉ AND SULTAN. Beitr. z. klin. Chir., 1902, xxxii, 492.

GARRÉ AND QUINKE. Lungenchirurgie. 1912, 2te Aufl., 127.

GHON. The primary lung focus of tuberculosis in children. J. and A. Churchill, London, 1916.

GIRON. Localisation pulmonaires par embolies septiques chez les blessés. Rev. gén. de clin. et de thérap., Paris, 1917.

HAMPELN. St. Petersburger med. Wchnschr., 1876, No. 40; 1887, No. 17.

HEWLETT. Monographic medicine. New York, 1916, i.

HILL. Brit. Med. Jour., Dec. 4, 1915.

HOFBAUER. Uebungsbehandlung des Lungenemphysems. Ztschr. f. diätet. u. physik. Therap., 1908, xi, 581.

HOOVER. The alveolar air and minute volume of air in pulmonary emphysema. Arch. Int. Med., Chicago, 1913, xi, 52-65.

HUBER. Pulmonary emphysema. Therap. Gaz., Detroit, 1913, xxix, 619-622.

KINNEAR. Brooklyn Med. Jour., Oct., 1897.

KISSLING. Ergebn. d. inn. Med. u. Kinderkrankh., 1910, xxxviii.

KRAUSS. Ueber eine besondere Form experimentele hervorgerufenen Lungenoedems. Berl. klin. Wchnschr., 1913, xxii, 1035.

LAMBERT. Four cases of primary carcinoma of the lung. Proc. New York Path. Soc., 1916, xv, 117-19.

LANZA. Jour. Missouri State Med. Soc., June, 1916, xiii, No. 6.

LENHARTZ. Verh. des Vereins der deutsch. Roentgengesellschaft. 1905, pp. 7-56.

———— Handbuch des praktischen Medizin. Ebstein u. Schwalbe, Bd. iv, 360.

LORD. Diseases of the bronchi, lungs and pleura, pp. 205 and 302.

———— Boston Med. and Surg. Jour., 1905.

MACKENZIE. Diseases of the heart. 3rd Ed., 333.

MANDEL AND GIBSON. Clinical manifestations and treatment of gas-poisoning. Jour. Am. Med. Assn., lxix, No. 23.

MATSUOKA. A contribution to the pathology of obstructive edema of the lung based on observations with the Starling heart-lung preparation. Jour. Path. and Bacteriol., 1915-16, xx, 53.

McMAHON AND CARMAN. Roentgen diagnosis of primary carcinoma of the lung. Jour. Am. Med. Sc., Feb., 1918, clv, p. 34.

MILLER AND DUNHAM. Am. Jour. Roentgenol., June, 1917, iv, 269.

MOORE. Roentgen diagnosis of bronchiectasis. Am. Jour. of Roentgenol., 1916.

NORRIS AND LANDIS. Diseases of the chest, p. 480.

OLIVER. Diseases of occupation, 1908.

OSLER. Practice of medicine, 8th Ed., p. 664.

PACKARD. Primary malignant neoplasm of the lung. Am. Jour. of Med. Sc., 1917, cliv, 351-365.

PEAT. The effect of gassing as seen at casualty clearing station. Jour. Can. Med. Assn., 1918, viii, 17-25.

PHEMISTER. Chronic lung abscess with pulmonary hypertrophic arthropathy. Surg. Clin. of Chicago, April, 1917, i, 381.

RAITHER. Studien über Emphysem. Monogr., Würzburg, 1912, p. 28.

REICHMANN. Heilung eines Falles von Lungengangrän durch künstliche Pneumothorax. München. med. Wchnschr., 1915, lxii, 1111.

ROSSBACH. Verhandl. des 6ten Cong. für innere Med., 1887, p. 217.

SCHALL. Beitr. z. Klin. d. Tuberk., 1910, p. 407.

SCHOMBERG. Zur Localisation der Lungenembolien. Centralbl. f. allg. Path., 1916, xxvii, 73-80.

SCOTT AND FORMAN. Primary carcinoma of the lung. Med. Rec., New York, 1916, xc, 452-55.

SHAW. A clinical lecture on gangrene of the lung. Lancet, London, 1914, i, 1095-98.
STRUEMPELL. Spezielle Pathologie und Therapie. 1909, i, p. 229.
SUDSUKI. Virchow's Arch. f. path. Anat., 1899, p. 438.
TSCHEKAN. Allg. med. Centr.-Ztg., 1904, p. 374.
UNDERHILL. Arch. Int. Med., June, 1919, xxiii, No. 6, p. 753.
VOLVENEL AND MARTIN. Clinical picture of gas-poisoning. Progrès. méd., Paris, 1917, 32-88.

CHAPTER IV

DISEASES OF THE PLEURA

By Charles P. Emerson, M.D.

Acute inflammatory diseases of the pleura and their sequelæ, p. 578:—Classification, p. 578—Acute fibrinous pleurisy, plastic pleurisy and dry pleurisy, p. 579:—Definition, p. 579; Etiology, p. 579; Symptomatology, p. 580; Diagnosis, p. 585; Sequelæ, p. 586; Association with other diseases, p. 586; Clinical varieties, p. 589; Treatment, p. 591; Prognosis, p. 592; Pathology, p. 593—Serofibrinous pleurisy, pleurisy with effusion, p. 593:—Classification, p. 593; Etiology, p. 594; Symptomatology, p. 595; Diagnosis, p. 607; Complications, p. 609; Sequelæ, p. 610; Clinical varieties, p. 610; Treatment, p. 611; Prognosis, p. 614; Pathology, p. 615—Empyema, p. 615:—Definition, p. 615; Etiology, p. 616; Symptomatology, p. 616; Diagnosis, p. 619; Complications, p. 620; Sequelæ, p. 621; Association with other diseases, p. 621; Clinical varieties, p. 622; Treatment, p. 627; Prognosis, p. 629; Pathology, p. 630—Hemorrhagic pleurisy, p. 630.
Non-inflammatory exudates within the pleura, p. 631:—Pneumothorax, p. 631:—Etiology, p. 631; Symptomatology, p. 635; Diagnosis, p. 642; Complications, p. 643; Sequelæ, p. 643; Association with other diseases, p. 643; Clinical varieties, p. 644; Treatment, p. 645; Prognosis, p. 646; Pathology, p. 646—Hydrothorax, p. 647: Etiology, p. 648; Complications, p. 648; Association with other diseases, p. 648; Treatment, p. 649; Prognosis, p. 649; Pathology, p. 649—Hemothorax, p. 649:—Definition, p. 649; Etiology, p. 649; Symptomatology, p. 649—Chylothorax, p. 649:—Definition, p. 649; Etiology, p. 649; Symptomatology, p. 650; Diagnosis, p. 650; Treatment, p. 650; Prognosis, p. 650.
Pleuromycoses, p. 650:—Actinomycosis of the pleura, p. 650:—Definition, p. 650; Etiology, p. 651; Symptomatology, p. 651; Complications, p. 651; Treatment, p. 651; Prognosis, p. 651; Nocardiosis (streptothricosis) of the pleura, p. 651.
Tumors of the pleura, p. 652:—Carcinoma of the pleura, p. 652:—Etiology, p. 652; Symptomatology, p. 652; Diagnosis, p. 653; Treatment, p. 653; Prognosis, p. 653—Primary sarcoma of the pleura, p. 653—Secondary malignant tumors, p. 653.
Echinococcus disease of the pleura, p. 654:—Etiology, p. 654; Symptomatology, p. 654; Diagnosis, p. 654; Complications, p. 655; Treatment, p. 655; Prognosis, p. 655; Pathology, p. 655.

General Classification.—The pathological conditions of the pleura and of the pleural cavity may be classified as follows:

1. Acute inflammatory diseases of the pleura (acute pleuritis) and their sequelæ (including hydropneumothorax and pyopneumothorax).

2. Non-inflammatory exudates within the pleura: pure pneumothorax, hydrothorax, hemothorax and chylothorax.
3. Pleuromycoses (infections due to organisms higher than bacteria).
4. Tumors and cysts of the pleura.

ACUTE INFLAMMATORY DISEASES OF THE PLEURA AND THEIR SEQUELÆ

Classification.—A classification of the acute inflammatory diseases of the pleura, based on gross pathology, is the only one which can meet the demands of clinical medicine. The classification on this basis follows:

1. Fibrinous, plastic or dry pleurisy, including diaphragmatic pleurisy.
2. Pleurisy with serous effusion (acute serofibrinous pleuritis).
3. Pleurisy with purulent effusion (empyema), including encapsulated empyema.
4. Hydropneumothorax.
5. Pyopneumothorax.
6. Obliterative pleurisy (thickened pleura).

Each of the above groups of conditions presents its own problems in diagnosis and treatment.

The scientific medical nomenclator would prefer a classification based on etiology, but, as applied to diseases of the pleura, such a one would have little value in clinical medicine. The clinician bases diagnosis and treatment on symptoms and physical signs, and these depend more on the gross pathology of the condition than on its etiology. For illustration, tuberculosis can cause each and every one of the six above-mentioned forms of pleuritis, and yet the problems of treatment of each are different. Streptococcus and tuberculous empyemas present more points in common for immediate therapy than do tuberculous fibrinous pleurisy and tuberculous empyema. In the discussion of prognosis and of later treatment, however, the value of an accurate knowledge of the etiology of the conditions will at once be apparent.

Former classifications listed the inflammatory pleuropathies as primary and secondary. This idea has in general been abandoned, because all forms are now considered to be secondary. But even if we grant that they are secondary, the current opinion is too extreme which entirely subordinates diseases of the pleura to diseases of the lung. It is true that there are no idiopathic pleurisies in the former sense, for all infections of internal organs are secondary, yet this is also true of many of the infections of the lung itself. The term primary pleurisy need not mean that the pleura is the first organ of the body to be infected, or that it alone has been infected; but, clinically, it indicates that the pleura is the first of the infected organs to give rise to recognizable symptoms and signs in a person who was previously apparently healthy. In this sense tuberculous pleurisies are often primary, relative to the subsequent pulmonary tuberculosis. Were this more generally granted, the mortality from pulmonary tuberculosis might be considerably reduced.

An old and popular classification of pleuropathies as acute, subacute and chronic is to be abandoned, since it is based on a mistaken idea of inflammation. It is now agreed that the connective tissue which forms in an infected organ is not itself due to an inflammatory process, but that it represents an attempt to repair the injury inflicted by the acute process. "Acute" is a valuable term when it is used to signify either the brief duration of an inflammation or its severe character, but the term "chronic" cannot always be used in contrast. An inflammation is acute so long as there is any active inflammation in progress, no matter how "chronic" its course may be. Certainly the term chronic should not be used to describe the results of repair in the inflamed area.

ACUTE FIBRINOUS PLEURISY, PLASTIC PLEURITIS AND DRY PLEURISY

Definition.—Acute fibrinous pleurisy, or acute pleuritis, is an acute superficial inflammation of the pleural surfaces caused by a variety of organisms. This inflammation leads to desquamation of the endothelium and to the formation in the subendothelial tissue of an inflammatory exudate consisting of more or less fibrin, with a relatively small amount of fluid. Such a process usually results in the formation of permanent adhesions which unite the opposed inflamed pleural surfaces.

As a type of this disease, that form of acute fibrinous pleurisy which is clinically called *primary dry pleurisy* will be first described, and then the differences between this form and others will be mentioned. Furthermore, this description will apply only to a pleurisy which involves the lower front and side of the thorax, since the symptoms and physical signs are distinctive only when the pleurisy is located in this region. It will at once be noted that the "typical" cases of fibrinous pleurisy are in a minority, since the same pathological process is much more apt to involve other areas of the pleural surface and to give rise to quite "atpyical" symptoms.

Etiology.—A pleurisy which would be primary in the sense formerly implied by the term *"idiopathic"* is, of course, not to be considered as possible, for the infection of the pleural sac, like that of all other internal organs, is possible only when pathogenic microörganisms gain admission to the body through a portal of entry and reach the pleura through the blood or lymph circulation, by trauma, or by direct extension from a neighboring organ. A "primary" pleurisy is one the symptoms of which interrupt a period of apparently good health, or one which seems to precede, or cause, or lead up to a later lesion. In these senses a pleurisy may be as primary as a pneumonia. "Secondary" pleurisy indicates clinically that the symptoms of involvement of the pleura follow and combine with or supersede the symptoms of involvement of another organ. During the last few years there has been a tendency to deny diseases of the pleura the attention they deserve, and to consider them rather as subordinate elements of more important disease groups. This is unfortunate, for it would seem to be true that pleurisy, in tuberculosis for example, may be primary, as well as secondary, to involvement of the lung.

The history of *exposure* to cold and wet is frequently obtained in cases of fibrinous pleurisy, and this relationship seems to be important in at least 10 per cent. of the cases. The patients giving this history, however, are not all strong, healthy-appearing persons, but usually give a history of *diseases of the cervical lymph-glands* or upper respiratory passages. These cases are common in young persons and develop especially during the winter months. Direct *trauma,* such as a fall or a blow on the chest, is frequently the immediate starting point of a fibrinous pleurisy. This is, in fact, one of the most important causes. In these cases one must assume the existence of a latent tuberculosis or pyogenic septicemia, perhaps from the tonsils, and the development in the pleura, as a result of the trauma, of a point of least resistance which affords a suitable nidus for the organisms in the circulating blood.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—If the period of incubation is to be defined as the time which elapses between the entrance of the infecting organism into the body and the appearance of the first symptoms of this infection, then seldom, if ever, can the term "acute fibrinous pleurisy" be used, since, in most of the forms of this disease, the body has probably already been harboring the infecting organism for years, and the pleurisy represents merely the invasion of the previously normal pleura. If, however, the term is to be defined as the time which lapses between the definite trauma, or the exposure which stirs up the latent acute infection of any other organ, and the appearance of the symptoms of involvement of the pleura, then the period of incubation may last but twelve or more hours. In these cases the pleurisy is to be considered, not as a new infection, but as the involvement of a new (previously normal) tissue in a person who has been harboring a latent, long-standing process to which his body has already gained considerable resistance, but which resistance was lowered by the trauma or exposure to cold and wet.

Prodromal Symptoms.—Few cases of fibrinous pleurisy show any prodromal symptoms, and yet in some the pleurisy is preceded by cough and expectoration, which would indicate an initial infection of the respiratory tract.

Mode of Onset and Course of the Disease.—In rare cases, the disease begins with a chill or with chilly feelings. Dry pleurisy of the lower front or axilla usually begins as "a stitch in the side," that is, a sudden, sharp pain in the chest, directly dependent on respiration. It seems to cut each breath short and is made worse by local pressure, by movement of the body, and especially by deep breathing or coughing.

During the few days which follow the onset, seldom extending over more than a week, the general symptoms are those of any acute infection: slight fever, headaches, anorexia and constipation. The local definite pain on respiration, together with the friction rub, slowly disappear, although a painless rub may sometimes persist and later even be palpable as well as audible. The fever and other symptoms slowly subside and leave the patient very weak, much weaker, in fact, than one would imagine, considering the mild appearance of his illness. The convalescence is usually slow. It may be assumed that in practically all cases the fibrous exudate undergoes organization, and that the resulting adhesions bind the pleural surfaces together to a greater or lesser degree. The prognosis, so far as the present illness is concerned, is good, but, generally speaking, the outlook must depend in no small degree upon the later course of that infection of which the pleurisy was but one manifestation.

At this point should be mentioned the differences—to be discussed at length later—between the pleurisy of the lower front and axilla and that involving other areas of the pleura. Pleurisy involving the upper thoracic zones seldom causes acute pain, but usually produces only a dull ache, often mistaken for arthritis of the shoulder-girdle, or a feeling of weight on the chest, while pleurisy involving the diaphragm may cause severe pains referred to the neck, shoulder or to the abdomen. In the latter case it is often mistaken for acute abdominal diseases.

Objective Symptoms.—Early in a case of dry pleurisy, involving the lower lateral or anterior thorax, almost every expression and motion of the patient indicates extreme pain, evidently associated with respiratory movements, inasmuch as the patient takes short, rapid, shallow breaths. He holds his affected side as immobile as he can; he avoids motion of his trunk; he leans toward the affected side, and presses it with his hand. It is evident that he fears to cough, almost to speak. This relative immobility of the affected side is not entirely the result of the voluntary efforts on the part of the patient to limit the excursion of the affected side, for it continues after the pain ceases. To a small degree it is an involuntary inhibition of the movement of the muscles of respiration near the diseased area controlled by a protective mechanism as yet little understood. One sees a similar limitation of motion over the upper chest of a person with early apex tuberculosis, often wrongly interpreted as a result of "fibrosis of the lung" or of "adhesions." This protective phenomenon can be easily observed in dogs in which pleurisy is being induced experimentally under light anesthesia. Dr. Ralph L. Lochry, of Indianapolis, told the author that, as a result of considerable experience during the influenza epidemic, he could determine through the fluoroscope the interspace in which an exploratory puncture had recently been made, by the approximation of the neighboring ribs due to local muscle spasm. Pleurisy involving the upper or posterior chest is much less painful, since there is less excursion of the lung on respiration. In fact, the patient may not associate his malaise with the organs of respiration, and yet he may give evidence of this reflex by a rapid, shallow breathing movement. An increased frequency of respiration is also a part of the fever complex and may run parallel to the temperature and pulse curves. There is seldom a true dyspnea and, when it is present, it is only slight.

Cough is a common early symptom of pleurisy, and, when typical, it is one of the distinctive features. It was present in 71 per cent. of Lord's cases. It is usually painful, short, hacking and dry, probably pleural in origin. In other cases, however, the patient raises a tract of sputum, while in a few cases (about 4 per cent.) the sputum is bloody. It may be assumed that in these cases the pleurisy is only a part of a more general infection involving the lung as well.

The temperature is but little elevated, in severe cases only rising to 102° F. (38.89° C.) or 103° F. (39.44° C.). It is irregular, yet seldom hectic. Later it slowly falls by lysis.

The pulse-rate is in proportion to the rise of temperature, and ranges about 100 per minute. It presents no unusual features.

Subjective Symptoms.—Chills or chilly feelings are felt early in some rather exceptional cases of fibrinous pleurisy.

Pain is the most constant and characteristic early symptom in cases involving the lower front or side of the chest, and is indeed almost the only subjective symptom. It is usually short, stabbing or cutting, and is often described as "a stitch in the side" which cuts each breath short. Sometimes it is excruciating in its severity, but this is seldom true. Such pain is definitely associated with respiratory movements. It is usually worse with inspiration, yet, in a few cases, it is present only with expiration. As a rule, it disappears in a few days along with the fever, although it may last for weeks. The lower down on the side or front of the chest the pleurisy is localized, the worse is the pain. This is due, for one reason, to the great excursion of the lung at that point on respiration. In other cases there is pain only when the patient coughs, takes a long breath, laughs, makes a sudden movement of the chest, or suddenly changes the posture of his body. Spontaneous pain is sometimes absent, in which case there may be tenderness on pressure over the infected area. It is absent also in patients at both extremes of ages.

It is well to mention at this point that in all cases of pleurisy the pain, wherever localized, is a referred pain. In most cases it will be localized accurately over the lesion, but not always. This may explain its greatest frequency in the nipple region and under the scapula, since, it is said, our ability to localize sensory impressions seems more highly developed at those points than elsewhere. This may explain also the cases with symptoms suggesting pleurisy, but in which we hear no friction at the spot where the patient localizes his pain, and also the few cases in which the pain is said to have been referred to the normal side of the chest.

Pain is seldom felt in the lower back, perhaps because there is less movement on respiration at this point and because enough pleural fluid may be present to prevent the friction-rub. Studies at autopsy leave no doubt that fibrinous pleurisy much oftener involves the apex of the lung than the lower anterior or lateral regions of the chest, and yet these cases are seldom recognized clinically. These patients complain merely of a soreness of the shoulder which they describe as "rheumatism," or of a dull heavy feeling over the chest not associated with breathing. The pain in diaphragmatic pleurisy is described later.

PHYSICAL FINDINGS.—*Observation.*—In a case of acute fibrinous pleurisy of the lower anterior or lateral regions of the chest every attitude and motion of the patient indicates that he is in pain. It is evident that he tries to limit the respiratory movements on one side of the chest. He may sit up holding the affected side with his hand, or he may bend his body to that side, or he may lie on the sound side, perhaps to relieve the inflamed pleural surfaces of the weight of the mediastinal organs and of the other lung. He may lie on the affected side, perhaps to limit the motion of the chest-wall in respiration. Whichever way the patient lies, he objects to a change of posture. If the pleurisy involves the upper regions of the chest, especially the apex, the patient may be quiet and express general discomfort, and yet be quite unconscious of any effort to keep quiet or to limit his respiratory movements, although it may be evident to the observer that he actually is doing so. The respiratory movements are shallow on both sides, but distinctly more limited in amplitude on the affected side.

Palpation.—By palpation we may sometimes make out the limitation of expansion of the affected side better than by inspection. Local pressure over the area of the suspected pleurisy tends to increase the pain on respiration and may elicit pain in the case of some patients who have had none on quiet respiration. General pressure, however, over a wide area tends to lessen the pain by decreasing the excursion of the chest.

After the acute process is over the examiner may feel with his hand an intense friction-rub of which the patient is quite unconscious unless he happens to place his own hand over that spot.

Percussion.—The note on percussion over the area involved in acute fibrinous pleurisy is often described as normal, and yet it is frequently slightly impaired. This impairment is often explained as being due to a thickening of the pleura by a recent fibrinous exudate or by old adhesions, but in some cases it seems to be caused by locally increased muscular tension of the chest-wall due to a protective reflex. It should be borne in mind that the note on percussion over the normal chest is a chest-wall note modified by the lung, rather than a lung-note modified by the chest-wall. Many modifications of the percussion note, usually attributed to changes in the lung, are, in fact, due to modifications in the physical properties of the chest-wall, brought about by the position of the body, local pressure, increased muscular tension, etc.

Later in a case of fibrinous pleurisy, however, enough exudate may cover the pleura to produce a slight impairment of the note on percussion.

Auscultation.—The most typical physical sign in fibrinous pleurisy is a superficial, faint, scratching, to-and-fro sound, most intense with inspiration, and increased by pressure. One hears this about one hour after the onset of the symptoms. In the early stages it can scarcely be heard. It may be audible over a very limited area, hardly larger than the bell of the stethoscope. It is louder on deep breathing and loudest, if present, where the excursion of the lung is the greatest. It is, therefore, most often heard on the lower chest in front or at the angle of the scapula. Sometimes this rub is not audible, even when the patient complains of a typical pain accompanying each breath, and even though one can elicit definite tenderness on pressure. A little later this rub becomes louder and may resemble the creaking of leather when bent. It will then occupy a much wider area. The friction is often jerky and inconstant, sometimes heard with one breath and not with the next, possibly owing to temporary fixation of the pleural surfaces. The localization of the pain is related to the seat of the pleurisy in the manner described above, but the place where the friction-rub is best heard will depend upon certain other factors not yet well understood. For example, the friction-rub of a pleurisy of the lateral chest-wall may be heard more plainly at the apex. Sometimes we hear no friction-rub in patients who give every other indication of a pleurisy. It may be that we do not listen at the right place. Sometimes we hear the rub in patients who complain of no pain, especially in the young and in the very old, and during the convalescence of acute cases.

Certain sounds closely resembling a friction-rub must be carefully differentiated. One such sound heard over the upper back is said to be due to crepitus at the shoulder-joint. Pleuropericardial sounds must be excluded.

Laboratory Findings.—A slight secondary anemia is to be expected. The leukocytes in 37 cases, which we reported, ranged in 24 cases from 10,000 to 22,900, while in 13 the counts were normal. Lord[1] found the count above 12,000 in 39 per cent. of his cases of fibrinous pleurisy. Since the count was above 12,000 in but 9 per cent. of his cases of pleurisy with effusion, he suggests that the higher count in fibrinous pleurisy is evidence that this condition is more often a pyogenic infection than it is in the other.

On tapping the chest in a case of fibrinous pleurisy, we usually get no fluid, although at the very base behind we may get a little, rather turbid and rich in leukocytes. The urine presents nothing abnormal.

Special Examinations.—The roentgenological examination of the chest in acute fibrinous pleurisy has considerable value. By this means we may exclude an unsuspected bronchopneumonia or a developing pleurisy with effusion. Later in the course of these cases this examination is of great value in determining the presence, degree and extent of the thickened pleura, and in watching for, with a view toward possibly checking, the development of deformities of the chest from contraction of the newly formed fibrinous tissue.

Diagnosis.—It is only fair to remark at the onset that it would seem that only relatively few cases of fibrinous pleurisy are, or can be, accurately diagnosed. For instance, the pathologist finds evidence of an old fibrinous pleuritis in 74.4 per cent. of the patients examined at autopsy while in the wards of the same hospital the clinicians make this diagnosis in but 2.7 per cent. of the patients admitted. Of course, the adhesions are the permanent record of long-standing lesions, while the possibility of the diagnosis of the acute condition would probably be present for only a few days. But apart from this, even during the week of the acute illness, the diagnosis of a pleurisy in a considerable area of the pleural surface would be difficult, perhaps impossible. The text-book picture of acute fibrinous pleurisy is that of an inflammation of the pleura opposite the lower front of the chest and axilla. There is some danger that even these typical cases may be confused with certain other conditions. Among them are intercostal neuralgia, pleurodynia, and neuralgia of the phrenic nerve. Neuralgia of the phrenic nerve has been described as a condition which causes intense pain over the lower thorax along the insertion of the diaphragm together with the presence of painful points which may be localized by deep pressure. This pain is intense on respiration, especially on full inspiration, coughing, etc. In the so-called intercostal neuralgia the pain is circumscribed, darting and paroxysmal. There is no fever. No friction-rub is heard. Tender points may be found along the course of the nerves at their points of exit. This may precede a herpes zoster. Another such condition is pleurodynia, a variety of myalgia involving the intercostal muscles of one side, especially the left, sometimes also the pectorals and the serratus magnus. This is possibly the most painful form of myalgia, inasmuch as each muscular movement increases it and rest of the muscles of the thorax is impossible. A deep breath or cough causes intense pain, which may shift its location even to the other side. There is also intense pain on pressure, sometimes over a very limited area. There is no fever. No friction-rub can be heard. The author describes these conditions out of respect to an authoritative medical literature. In the light of more recent progress, many of these cases would possibly be better described as acute spondylitis, pleurisy, etc.

In case the fibrinous pleurisy involves the apex of the lung the condition may produce no characteristic symptoms whatever; or it may cause only a dull ache in the shoulder, suggesting an arthritis; this is often called "rheumatism." In fibrinous pleurisy of the diaphragm we have an intensely interesting problem in diagnosis. If the peripheral zone of the front and lateral regions of the diaphragm is involved, then the pain is referred to the upper abdominal region and is often interpreted as being due to disease of the upper abdominal organs, e.g., appendicitis or gall-stones; or, again, if the posterior portion of the diaphragm is involved the pain would be referred to the back, possibly throughout the entire lumbar region, and a diagnosis of spondylitis or lumbago, floating kidney, etc., may be made. If, on the other hand, the dome of the diaphragm is involved, the pain is in the neck and there is danger that a diagnosis of an angina pectoris or cardialgia may be the result.

It is sometimes difficult to exclude pleurisy with effusion, especially if the fluid is small in amount and lies between the diaphragm and the lung. Again, we may have a fibrinous pleurisy combined with pleurisy with effusion, the former lying anterior and the fluid posterior; or we may have a hemorrhagic pleurisy at one portion of the chest and a fibrinous pleurisy at another.

Fibrinous pleurisy is a common complication of other acute infections, as, for instance, acute lobar pneumonia, pulmonary tuberculosis, tertiary lues, spinal diseases, pulmonary tumor, lead-poisoning, caries of the rib, periostitis of the rib or the spine, or thoracic aneurysm.

Sequelæ.—A fibrinous pleurisy, it is said, may clear up entirely, leaving the pleural surfaces smooth and free of adhesions; but surely such cases must be rare. The rule would seem to be that any definite infection of the pleura leads to adhesions between the denuded areas. These adhesions, however, are often unsuspected. Indeed, it is remarkable how widespread may be the adhesions, how completely the pleural cavity may be obliterated, in a patient quite unconscious of his condition, and how few and unsatisfactory may be the physical signs on examination. If the adhesions are few in number, their signs on physical examination may be absent or at least inconstant. The diaphragm phenomenon will be absent if the adhesions involve the anterior costophrenic sinus. In other cases there is slight limitation of the respiratory movements, slight impairment of the note on percussion and often a disproportion between the excursion of the chest-wall and the breath sounds. And yet all these signs are inconstant. Later, the adhesions, by contracting, may lead to deformity of the chest of greater or lesser degree. It is not uncommon to see vasomotor phenomena in cases with fibrinous pleurisy involving the upper chest, such as flushing of one cheek, unilateral sweating, dilatation of the pupil on one side, etc.; all these are due to the involvement of the cervical sympathetic system.

Sclerosis of the lung may follow fibrinous pleurisy. This is due to the invasion of the lung by the scar-tissue of the thickened pleura. This explains the pleurogenous interstitial pneumonia of Charcot.

Pleurisy with effusion or empyema sometimes follows a fibrinous pleurisy, but not in over 2 per cent. of the cases. There is little evidence to support the contention of some that fibrinous pleurisy is only a mild form of that disease, which naturally tends to develop into pleurisy with effusion.

Association with Other Diseases.—TUBERCULOSIS.—A primary dry pleurisy, it is said, should always be regarded as probably tuberculous in character. In these cases of early tuberculosis, the apex especially is involved. The pleurisy is usually quite extensive and the friction-rub, when heard, may continue for a long time. This and pulmonary hemorrhage are the two most common modes of acute onset of pulmonary tuberculosis. This pleurisy is supposed to be a conservative process, and it is useful since it tends to prevent the later development of pneumothorax.

A second form of tuberculous pleurisy is the acute variety which develops in cases of chronic pulmonary tuberculosis. These are apt to run a long course.

Third, acute tuberculous pleurisy may appear as a secondary infection in other chronic infections and be an important complication, even a terminal infection, in persons with such chronic diseases.

A fourth type, the chronic tuberculous adhesive pleurisy, or the so-called primary proliferative pleurisy, may lead to great thickening of the pleural membranes and to secondary invasion of the lungs by scar-tissue.

A fifth clinical type is the fibrinous pleurisy, leading to adhesions between the pleuræ, which accompanies practically all cases of chronic pulmonary tuberculosis.

In fact, the great majority of cases of the so-called primary dry pleurisy are tuberculous infections of the pleura. Indeed, in the absence of other causes, we may assume this to be true of each case. The tuberculosis of the pleura itself will probably develop no further. It is the spread of the disease to other tissues which is important. Of 5,895 cases of pulmonary tuberculosis, 23.8 per cent. gave a history of pleurisy as one of the early symptoms. Active tuberculosis of the lung can be demonstrated as coincident with the fibrinous pleurisies in only 5 per cent. of the cases, while active pulmonary tuberculosis and serofibrinous pleurisy coëxist in 13 per cent. of the cases of the latter disease. "This," says Lord, "may be proof that the tuberculosis causing the fibrinous pleurisy is apt to be less advanced" (than in the cases with effusion). In many cases of latent tuberculosis the primary infection is one of the lymph-glands with which the serous sacs are intimately related. It seems that in many cases the infection of the pleura is an intermediate step between the glands and the lung. It is more than possible that, if we considered this possibility in our treatment and did not wait for the development of active intrapulmonary diseases before beginning aggressive treatment, we could forestall many a case of phthisis.

Focal Infection.—The importance of focal pyogenic infections in tonsils, teeth, nasal sinuses, etc., in the causation of fibrinous pleurisy cannot be doubted, nor does this lessen the importance of tuberculosis as the primary disease, for in chronic tuberculosis of the glands or lungs the progress of the case, its acute exacerbations, etc., depend in no small degree upon secondary streptococcus infections. If these are controlled, tuberculosis is controlled to a greater or lesser extent. It is of interest that fibrinous pleurisy, so often tuberculous, resembles a mixed infection more than does serofibrinous pleurisy; the infiltration of the subserous tissue with pus-cells, the few cubic centimeters of cloudy pleural fluid, the more frequent leukocytosis, etc., suggest this.

A pleurisy, usually fibrinous, is the rule in case any disease of the lung reaches the pleura. The pulmonary diseases important in this particular are pulmonary tuberculosis, pneumonia, bronchopneumonia, pulmonary abscess, gangrene, hemorrhagic infection, mycotic infections, etc. A fibrinous pleurisy may be expected in case any inflammatory diseases of a neighboring organ, such as diseases of the pericardium, abdomen, mediastinum or chest-wall, reach the pleura. Fibrinous pleurisy may represent one localization of the multiple infections caused by septicemia, such as septic tonsilitis, endocarditis, pericarditis, arthritis, typhoid fever, etc. It is also important as a complication of, or as a terminal infection of, chronic systemic diseases such as gout and nephritis, and, in fact, any disease which leads to asthenia. The bacteria involved are *Bacillus tuberculosis,* the streptococci, pneumococci, etc.

ACUTE LOBAR PNEUMONIA.—Acute lobar pneumonia which reaches the surface of the lung is practically always complicated by an acute fibrinous pleurisy. This may consist merely of a turbidity of the membrane, or of a thin sheeting of exudate which causes a slight thickening of the pleural membrane, or of a very thick layer of creamy fibrin and pus. This pleurisy is absent in central pneumonia and may be absent or slight in apex pneumonia.

In a second group of cases an acute pleurisy is the earliest symptom of the pneumonia. These patients complain of sudden agonizing pain in the side accompanied by a short, dry, painful cough, and by pain on respiration. The illness seems to be more severe than the signs would indicate. Pneumonia is not suspected until the more marked symptoms of pulmonary consolidation and the rusty sputum make their appearance.

There is still a third clinical group of cases of acute lobar pneumonia which begin as fibrinous pleurisy and lead to frequent and serious mistakes in the surgical wards. The author refers to cases in which the cough is at first absent or inconspicuous, and in which the pain is referred to the lower abdomen on the right side. It is not at all rare for these cases of pneumonia to be interpreted and treated as appendicitis. Many of them, doubtless, are interpreted later as ether-pneumonias.

The following pulmonary infections are often accompanied by fibrinous pleurisy: bronchopneumonia (in the case of influenzal bronchopneumonia, however, the exudate is more often serofibrinous, or purulent, than fibrinous), chronic bronchitis, chronic fibrinous bronchitis, mycotic infections of the lungs, cancer, abscess or gangrene of the lungs, pulmonary infarction, etc. Again, a fibrinous pleurisy may be the direct extension of a pericarditis, a mediastinitis, or of an inflammation of the liver.

Fibrinous pleurisy often represents the first localization of the infection in severe cases of the specific fevers. The so-called pleurotyphoid form of typhoid fever may pass for several days as simple fibrinous pleurisy, until other features call attention to the true nature of the condition. Fibrinous pleurisy has been found in from 2 to 8 per cent. of the cases of typhoid fever which reach autopsy. In many other diseases which begin as a general septicemia, especially the severe cases of these fevers, the pleura may easily be involved by way of the blood.

Among these may be mentioned acute bacillary dysentery; cerebrospinal fever, in which it is not uncommon; smallpox, in some epidemics of which fibrinous pleurisy is a marked feature; Asiatic cholera; trichiniasis; erysipelas, etc. Fibrinous pleurisy is an important terminal infection in cases of gout, in cardiovascular renal diseases, and in cirrhosis of the liver. In these terminal infections the organisms which cause the pleurisy are usually of the streptococcus group, but the pneumococcus, staphylococcus, gonococcus, proteus, *Bacillus pyocyaneus,* and the gas bacillus are also encountered, while acute tuberculous pleurisy is not a rare form of terminal infection.

Clinical Varieties.—Depending upon the localization of the infection, the clinical features of cases of fibrinous pleurisy differ considerably. The author speaks of pleurisy of the lower anterolateral thorax as the typical form of fibrinous pleurisy, since this is the type described in the text-book, although it is not the commonest form; apical pleurisy is important because of its frequency, its latency and the danger of a mistaken diagnosis.

DIAPHRAGMATIC PLEURISY.—Diaphragmatic pleurisy is important because of its frequency, of the difficulties inherent in its diagnosis and of the danger that error in diagnosis may lead to operation or other radical therapeutic measures. The pleura of the diaphragm may become infected from the visceral pleura, or from the abdomen. Capps,[2] in an interesting series of observations on 75 persons with pleurisy with effusion, determined that the visceral pleura is practically without pain sense, while the parietal pleura of the chest-wall is richly supplied by the intercostal nerves, and that referred pain from this area is sharply localized directly over the spot irritated. The anterior and lateral portions of the peripheral zone of the diaphragm, a band from two to three inches wide, and posteriorly, about one-third of the diaphragm, is supplied by branches of the lower six intercostal nerves. Stimulation of this area causes pain referred to the lower thorax and upper abdomen or to the whole abdomen on the same side, in the areas of the seventh to the twelfth thoracic spinal segments. The pain sometimes radiates to the flanks. The pain from irritation of the posterior diaphragm is referred to the upper back on the same side, or, sometimes, over the entire half of that side of the back from the ribs to the ilium. The central portion of the diaphragm and also the pericardium is supplied with sensory branches from the phrenic nerve. Pains originating in this area are referred to the region of the third and fourth cervical segments, that is, to the neck, especially the skin over the ridge of the trapezius.

The pains due to pleurisy are true referred pains, are spontaneous, accompanied by hyperesthesia of the skin, usually quite marked, and by hyperalgesia of the superficial tissues on pressure. Since the same pleuritis may involve both the intercostal region and the phrenic area, we are very apt to experience pains in several of the above-mentioned areas.

Pain referred to the skin over the lower thorax is severer than the physical signs would indicate, since the excursions of the lung and diaphragm are maximal at this point during respiration. The pain referred to the upper abdomen simulates abdominal diseases. Of the 61 cases reported by Capps, gall-bladder disease was suggested in 10, while in 15 the pain was referred to the region of the navel. Kelly and Weiss[3] reported 22 cases of diaphragmatic pleurisy, and among the diagnoses suggested by the pain in these cases were renal stone, gall-stones, acute cholecystitis, perforated gastric ulcer and acute appendicitis. Other cases with pain in the back suggest spondylitis or lumbago. It is said that the skin and muscles of the abdomen in the area to which the pains are referred are more sensitive to pressure in cases of diaphragmatic pleurisy than in those of acute abdominal diseases, and that the cutaneous reflexes are more active over the areas of referred pains. In both we have on pressure moderate rigidity of the abdominal muscles, covering the area of the referred pains. This rigidity may be even board-like. In diaphragmatic pleurisy the onset is acute, the relief, later, is complete, and the pain is increased by cough, by exertion, or by pressure along the tenth rib, ''yet in diaphragmatic pleurisy deep pressure over the painful area of the abdomen does not increase the pain as much as it would over an inflamed organ."

In discussions on differential diagnosis, perhaps too much emphasis has been laid on these pains as referred pains. After all, there is not a very great difference between a pain in the gall-bladder or appendix regions due to diaphragmatic pleurisy and one due to acute diseases of these organs. In all these cases the pains are true referred pains. The pain on pressure over an acute appendix without a peritonitis involving the anterior abdominal wall is not actually produced in the inflamed organ; this may be easily proved during operation under local anesthesia. The pain produced on examination is a referred pain, referred usually to the anterior abdominal wall at the point where we are pressing, but it is often felt in areas at some distance; it may even be referred to the left side.

In diaphragmatic pleurisy involving the dome of the diaphragm, the pain is referred to the neck and shoulder, sometimes suggesting cardialgia or angina pectoris. This is often associated with pain on pressure in the back below the twelfth rib on the same side. In one-third of the cases the pain in this region is spontaneous, while in other cases (Kelly and Weiss) it is elicited only by pressure and may then be severe, even though spontaneous pain is absent. In a suspected case, therefore, tender points should be searched for along the trapezius. This pain in the neck is made worse by coughing and by deep pressure. Sharply localized pain in the neck, spontaneous or only on deep pressure, and on the same side as the abdominal pain, indicates involvement of the dome of the diaphragm. Similar symptoms are met with when the pericardial pleura is involved. The diaphragmatic pleura of the right side is involved twice as frequently as is that of the left.

It is of great importance to note that other signs of infection of the respiration tract occur with diaphragmatic pleurisy. Such are increased rate of respiration, short breaths, cough, sputum, leukocytosis, sometimes herpes, respirations strictly thoracic and sometimes hiccough (2 of 22 cases, Kelly and Weiss; 5 of 61, Capps) which is quite intractable to treatment and ceases spontaneously. Nausea and vomiting are rare. The friction-rub was heard in 7 out of 22 cases, the clearest sound being obtained in the lower axilla.

PRIMITIVE DRY PLEURISY.—Primitive dry pleurisy may be clearly secondary to fibrinous pleuritis or to other manifestations of disease, usually some form of tuberculosis, or it may develop insidiously as a primary condition. In these so-called primary cases the first evidence to the patient of his disease may be the accidental discovery with his hand of a definite friction-rub. This form of pleurisy will lead to adhesive pleuritis, even to universal adhesions. In the secondary form the two layers of the pleura are greatly thickened, being even 2 and 3 millimeters in thickness, and contain firm fibrous and caseous masses enclosing small tubercles, and united by reddish-gray fibroid bands of tissue. The thickened pleura is often infiltrated by serum. The trouble may be local, may involve most of one pleura or both, or may be associated with a similar condition of the pericardium and peritoneum.

Some authors attempt to make a distinction between dry pleurisy and fibrinous pleurisy, on the ground that in the latter there is a little more fluid exudate, that the disease is not as patchy and involves a wider area, and that it is not quite so often tuberculous in origin as is the primary dry pleurisy but is more often due to the pyogenic infections. The best illustration of fibrinous pleurisy which they give is that which covers the involved lobes in acute lobar pneumonia. On physical examination in dry pleurisy, it is claimed, the dulness on percussion is more easily demonstrated and the friction-rub is heard over a wider area than in the fibrinous variety. The only real difference, however, between these forms of pleurisy would seem to lie in the intensity of the infection.

Treatment.—It is very important that the patient **rest in bed** during the febrile period of the disease and later resume his active life slowly, returning to bed in case of a recurrence of the fever. During the febrile period the **diet** should be that of any acute infection: six ounces of fluids every two hours (milk, sweet or buttermilk, egg albumen, fruit juices, etc.). The patient should be well **purged.** For local relief, **heat** or **cold** are both valuable. An **ice-bag** or strips of linen, chilled on a cake of ice and frequently changed, have given good results. Others prefer a **hot-water bottle**, a mild application of a **Pacquelin cautery**, or exposure to the heat of an electric light. The latter is superior to the Pacquelin cautery and can be applied handily in any household. A lighted sixteen-candle-power carbon filament globe on a free wire is stroked rapidly over the skin. **Fixation** of the chest often brings relief, and yet not always, especially in cases in which the diaphragm is involved. To accomplish a satisfactory fixation while the patient is in bed, a binder with shoulder straps is to be preferred to the long strips of adhesive plaster so often applied. The latter method certainly does not present enough advantage over the binder to offset its disadvantages, e.g., the interference with proper clinical examinations during the acute stage of the disease. And yet after the patient is up and about these strips of adhesive plaster are very satisfactory. They should be about four inches wide, long enough to extend over to the normal side both in front and behind, and should be applied during forced expiration. In diaphragmatic pleurisy the binder should fix the upper abdomen as well as the lower thorax.

During the acute period of the disease **morphin** must often be resorted to for comfort. Some feel that this is more potent if injected directly over the area of the pain. Cetrangolo[4] claims to be the first to have applied topical medication to superficial pleurisies in the form of **artificial pneumothorax.** He injected 100 c.c. of air (sometimes medicated with the vapor of camphorated oil) into the pleural cavity directly over the diseased area. He claims that his results were satisfactory.

During convalescence the patient seems to return unusually slowly to his accustomed health. One should always have the possibility of a future pulmonary tuberculosis in mind and treat his patient exactly as he would if such a diagnosis had been made; that is, he should require long **rest in bed,** long **vacations,** and the **avoidance of physical and mental fatigue and worry.** Since a secondary infection can keep active any latent infection, whether due to the same or to a different organism, all portals of entry, such as **infected tonsils** or teeth, should be **removed** and infected nasal sinuses should be **drained.** The diet for months should be abundant and rich in fat.

Deformity of the chest from the subsequent contraction of the fibrous tissue of the organized pleural exudate is seldom noticeable following simple fibrinous pleurisy, and yet it does occur, especially in children. **Pulmonary gymnastics** should be cautiously employed, especially deep breathing with the normal side partly fixed.

Prognosis.—With regard to immediate recovery the prognosis is practically always good; the ultimate prognosis, however, is grave, since so many patients develop pulmonary tuberculosis later. This is true of about 30 per cent. of the cases. On an average, this condition develops from four to five years after the attack of acute pleurisy. It is said, however, that an early fibrinous pleurisy indicates a good prognosis so far as a subsequent pulmonary tuberculosis is concerned, since it is a conservative process. If, as the author believes to be true in many cases, the infection in tuberculosis actually progresses from the supraclavicular or axillary lymph-glands to the pleura and from there to the lung, then the pleurisy assumes much greater importance than a mere "manner of onset of pulmonary tuberculosis," for its early treatment may prevent the pulmonary involvement.

The prognosis concerning function is good, although fibrinous pleurisy is nearly always followed by adhesions. At least 25 per cent. of the patients complain later of pain in the chest, which is sometimes only nagging, but is sometimes severe.

Pathology.—In the earliest stages of fibrinous pleurisy there is the so-called "lack-luster" appearance of the pleura; that is, the visceral pleura, first, and then the parietal pleura, lose their glistening appearance and become dull and congested, coarsely or finely granular, grayish-white in color, or reddish or red in color when ecchymoses are present. The area of pleura thus involved is later covered with a layer of fibrin, the thickness of which varies from a thin film to one almost one inch thick. This exudate usually extends into the interlobular fissures. The pleural cavity always contains an increased amount of cloudy fluid. Microscopical examination shows that the endothelial cells of the pleura are degenerated or gone and that the subserous tissue is swollen with serum and infiltrated with an increased number of polynuclear cells, while the lymphatics and blood-vessels are distended. The process may be limited to a small area, or, it may involve the whole of one side. Anatomically, fibrinous pleurisy most commonly involves the posterior aspect of the apex of the lung, a situation in which it is least often recognized clinically. The next most common point of localization is the lower lateral thorax, and it is here that the clinician observes the greatest pain, and most frequently hears a friction-rub. In this region the part most involved is the area of the fourth, fifth and sixth ribs between the parasternal line and the midaxilla. Not infrequently the diaphragmatic pleura, also, is involved. In a mild case the process may clear up entirely, the fibrin undergoing a fatty change and then finally disappearing, or the exudate may organize with the formation of adhesions. In the cases which clearly accompany tuberculosis of the lung, the adhesions are usually very firm at the apex; elsewhere they are delicate and lace-like in patches. They may form a membrane from 2 to 5 mm. thick. The lung itself may be the seat of extensive sclerosis, an "interstitial cirrhosis," which is the result of the dry pleurisy. This leads to the formation of dense strands of scar-tissue directly connected with the thickened pleura and which invade the lungs. The interstitial tissue of the lung then increases, transforming this organ to a greater or lesser degree into a dense mass of scar-tissue. In a case of old thickened pleura, it may be necessary at autopsy to cut or tear the lung free because of adhesions which may have obliterated the entire pleural cavity.

In these cases which accompany pneumonia or pyogenic infections, we are more apt to find at autopsy the most of the pleural cavity obliterated.

Serofibrinous Pleurisy—Pleurisy with Effusion

Serofibrinous pleurisy is a type of pleuritis characterized by the formation within the pleural cavity of large amounts of serofibrinous exudate. In all forms of pleuritis there is some increase of fluid, but in this type the clear, yellow exudate tends to keep the pleural cavity full.

Classification.—The first or tuberculous group includes about 63.4 per cent. of all cases. While at first there is nothing to suggest the nature of the infection, yet nearly all of them later prove to be tuberculous in character. The group second in importance is composed of cases due to infections other than tuberculosis, which infections, if more intense, would doubtless produce a purulent exudate. These first two groups are well-defined. The third is a small, heterogeneous group of cases due to a variety of causes.

Etiology.—In rare cases, pleurisy with effusion occurs, however, in patients whose previous health has been excellent. As a rule these patients present a history of slight malaise, of loss of weight, a tendency to bronchitis, etc.

In Osler's group of 194 cases, 161 were males and 33 females. Of these, 20 were under twenty years of age, 59 were between forty and fifty and 18 were over sixty.

PREDISPOSING CAUSES.—In general the predisposing factors would seem to be identical with those important in connection with early pulmonary tuberculosis. Of the immediate causes *exposure to cold* is the most important predisposing agent, since the collection of fluid sometimes rapidly follows a sudden wetting or a chill.

The close association between pleurisy with effusion and *tuberculosis* is shown by the fact that of the 5,895 cases of pulmonary tuberculosis reviewed by Norris and Landis, 23.8 per cent. gave a history of previous pleurisy.

EXCITING CAUSES.—*Bacteriology.*—Most of the cases of pleurisy with effusion are due to *Bacillus tuberculosis.* Evidence of this may be found at autopsy in 24 per cent. of cases. Tuberculosis can be demonstrated at autopsy elsewhere in the body in 15 per cent. of the cases (Osler). The excess of lymphocytes in the fluid suggests this infection. The tuberculin reaction has been positive in 76.5 per cent. of the cases. *Bacillus tuberculosis* can be demonstrated in the fluid in a large number of cases. This can be done directly by smears made of the fluid in but 2 per cent. of the cases (Netter); by inoscopy in from 20.8 to 55 per cent.; and by guinea pig injection in from 62+ to 85 per cent. (Lord.) The subsequent history often proves the relationship to tuberculosis, since 29.7 per cent. of the 562 cases observed by Hamman later developed tuberculosis. We may therefore say that of the cases of so-called primary idiopathic pleurisies with effusion, over 50 per cent., at least, are definitely tuberculous.

Of the non-tuberculous cases with serofibrinous exudate 5.2 per cent. are due to the pneumococcus. These pleurisies are usually secondary to pneumococcus diseases of the lung, although the failure to demonstrate this may sometimes seem to justify the term, "primary pneumococcus serofibrinous pleurisy." We must, however, remember that tuberculosis of the lung may be complicated by pneumococcus infection of the pleura. In pneumococcus pleurisies the fluid is sometimes serofibrinous at first, then turbid, due to fibrin flocculi, then definitely purulent. In many cases of acute lobar pneumonia there is an increased amount of fluid in the chest, and this is usually serofibrinous in character. The onset in pneumococcus serofibrinous pleurisy often resembles that of acute lobar pneumonia. The outlook in these cases is usually good.

Serofibrinous pleurisy occurs in connection with certain other diseases; 0.9 per cent. was associated with an acute rheumatic fever; 0.8 per cent. with trauma; 0.5 per cent. with typhoid fever. (Of 1,500 cases of typhoid fever reported by McCrae there was serofibrinous exudate in 3, that is, in 0.2 per cent.) Other cases have been reported associated with bronchopneumonia, pulmonary infarction, pericarditis, malignant endocarditis and uterine sepsis. In such cases the fluid is generally purulent. As explanation of its serofibrinous character in these cases, it may be assumed that the number of infecting organisms was small or that they had a diminished virulence, or that there was an unusual resistance on the part of the patient. Other organisms found are the streptococcus, Friedländer's bacillus, *Bacillus typhosus* and *Bacillus diphtheriæ*.

Symptomatology.—CLINICAL HISTORY.—A case of the so-called primary serofibrinous pleurisy of the first group mentioned on p. 594 will be selected as a type. The period of incubation is not known. The infection probably reaches the pleura by direct extension from a tuberculous focus in the lung or from some tuberculous gland in the neck, the mediastinum or axilla.

Prodromal Symptoms.—These are not uncommon and usually manifest themselves in patients who have had a slight cough and who have been in failing health for months.

Mode of Onset.—In very few cases, the onset is abrupt. These patients first have a chill, sometimes of great severity; this is followed by a severe pain in the side and by fever. The severity of the onset in such cases may, even in the absence of rusty sputum, justify the suspicion of acute lobar pneumonia. In more cases, however, chilly feelings are much more common at onset than are definite chills.

In over one-half of the cases, including most of the young and of the aged, the disease begins insidiously. These patients may have been losing weight for a long time. They feel ill, but cannot locate their trouble. They complain of weakness; they fatigue easily. They have from the first a slight fever, a rather rapid pulse, a little dyspnea and an increasing pallor. The temperature, which from the first tends to be irregular with morning remissions, rises higher and higher as the fluid accumulates, after which it may remain elevated during the fastidium of the illness. It then gradually becomes normal and may remain so during the period of absorption. Mild cases run a febrile course of from seven to ten days, at the end of which time the cough stops, the pain ceases and the fluid begins to absorb rapidly. If enough fluid has accumulated to reach as high as the fourth rib, however, convalescence is much slower. In some cases on first examination the fluid is up to the clavicle, and yet the patient is unable to give any data by means of which the duration of its presence can be determined. As a rule the febrile period lasts from one to three weeks; however, in untreated cases, i.e., in cases in which the fluid has not been removed by aspiration, it may continue for many weeks. Spontaneous absorption of the fluid is the rule, even in untreated cases, but in some the chest may contain fluid for months. It is only fair to state, however, that this is true in some cases also which have been tapped repeatedly.

In a few untreated cases the fluid ruptures through the lung or through the chest wall and recovery thus follows, while in still others it becomes purulent, and the case is then one of empyema.

Even though the exudate is large in amount, some cases are remarkably latent in their development, e.g., those following an acute lobar pneumonia, or those developing in the course of pulmonary tuberculosis. In these cases the fluid may be accidentally discovered during a routine physical examination, or by the pathologist on the autopsy table.

Objective Symptoms.—A patient with a pleural effusion almost filling the chest may be ill enough to be confined to his bed, and yet be quite ignorant as to which part of his body is involved. He is pale and often cyanotic; his respirations are rapid, and his pulse rather fast. Usually he feels more comfortable while sitting up in bed because this possibly prevents the volume of the fluid from hampering respiration, or because its weight lowers the diaphragm and gives relief by increasing the capacity of the chest. Or, he may lie on his affected side. If the effusion is small the patient may prefer to lie on his good side or to lie flat on his back. It is not clear why this last posture is assumed. These patients look much sicker than they seem to feel. Their respirations are rather rapid, and if the chest is full there may be a true dyspnea, and yet even when the chest contains considerable fluid this condition may be absent except on exertion. Pain is a rare feature; it is sometimes noticeable early while a fibrinous pleurisy is present, during which period it may be spontaneous or elicited only on pressure. Cough, pleural in origin, is an early feature of these cases. It is less distressing than is that of pneumonia, is less frequent, is short and dry, as a rule, while in 15 per cent. of the cases reported it has been absent. The sputum, if any at all is raised, is scanty, and is mucoid in character, but in about 2 per cent. of the cases it is blood-streaked; this suggests a concomitant pulmonary disease. A friction-rub may be heard above the fluid early in the diseases, and again later during the fluid's absorption. It may be evident on palpation. It often sounds like creaking leather, or, in other cases, it somewhat resembles the crepitation of an acute lobar pneumonia.

Cases of pleurisy with effusion are accompanied by more fever than are those of fibrinous pleurisy. The temperature seldom rises as rapidly or to as high a point as it does in pneumonia, its average being between 102° F. (38.8° C.) and 103° F. (39.4° C.). Later (and this is particularly true of old persons) it may be subnormal. In most cases it is normal in from seven to ten days from the onset, and yet the fever may persist for weeks, in which case intrapulmonary disease should be suspected. The surface temperature of the affected side is higher than that of the normal side. The pulse presents nothing of special interest, its rate being approximately that which one would expect in a case of fever of the degree present. Dyspnea is more infrequent than one would expect. The respirations are short and quick at first, especially if there is pleural pain. Later they are more normal and become hurried only on exertion. The early increase in the rate of respiration is due in part to fever, in part to pain, and in part to a protective spasm of the respiratory muscles evidently intended to immobilize the chest. Later, after the effusion has collected, the increased rate is due in part to the decrease of respiratory volume. In the early stages the respiratory rate relative to pulse and temperature is less disturbed than it is in pneumonia. If the development of the effusion has been rapid, a marked dyspnea, even orthopnea may result; whereas, if the effusion has been slow in collecting, there may be no dyspnea, provided the patient lies comfortably in bed, even though the chest is quite full. Toxic symptoms are not conspicuous. The patient may be hoarse from pressure on the recurrent laryngeal nerve. Dysphagia may result from pressure on the esophagus. Singultus is rare except in cases with diaphragmatic pleurisy.

Subjective Symptoms.—Pain in the side is the most typical and most distressing of the early symptoms. It is present in at least 89 per cent. of the cases and is entirely absent in about 5 per cent. It is generally referred to the region of the nipple or lower axilla, while, in other cases, it is referred to the back or to the abdomen. It is usually associated with tenderness on pressure over the painful area. This pain is lancinating in character and is much aggravated by coughing. Later, after the development of the effusion, it may be quite absent.

PHYSICAL FINDINGS.—*Observation.*—Immovability of the affected side is an early and important sign. This is due not alone to lack of respiratory volume but also to a protective mechanism which inhibits the movements of the affected side. The respiratory volume of the chest does not diminish in direct proportion to the amount of fluid present. The flattening and descent of the diaphragm will make considerable room for the effusion and there is also, as can be seen in the ward and confirmed in the laboratory, an automatic compensatory increase in the volume of the chest when fluid is introduced. This is accomplished by a change in balance in the intercostal muscles as well as by a lowering of the diaphragm. The immovability of the affected side of the chest is also due to the limitation of motion which is caused by pain, when it is present, and, later, by the above mechanism. The skin of the affected side is sometimes shiny and smooth. It is often slightly edematous. The surface veins are occasionally dilated, although this condition is rare.

The affected side shows a distinct increase in volume and the shoulder on this side is higher. This increase in size may be confirmed by mensuration, and yet it is more apparent than real. The intercostal depressions are obliterated and the spaces seem wider and often fuller than normal. In other diseases in which a limitation of motion is due to pulmonary lesions, a distinct diminution in the capacity of the chest is usually observed.

The apex-beat of the heart will be dislocated early. This is one of the most important of the physical signs. If the effusion is on the right side it may be in the fourth interspace beyond the mammillary line, or even in the axilla; while, if the effusion is on the left side, the apex-beat will be found near the ensiform, even on both sides of the lower sternum. In pleurisy with effusion this beat has never been reported to the right of the mediastinal line. The effusion sometimes pulsates (pulsating hydrothorax) although this condition is rare as compared with pulsating empyemas. Dilatation of the alæ nasi on respiration is less conspicuous than in pneumonia. There is not often dyspnea, marked cyanosis is rare and herpes is seldom seen. The pupils are often unequal, the one on the affected side being the larger. The absence of Litten's sign is of considerable value.

A small effusion in a chest which is free from adhesions will be found in the posterior inferior part of the chest, below the level of the lung. An effusion of 250 c.c., or less, in an adult, may escape detection on physical examination, for it requires a larger volume than this to diminish appreciably the volume of the lung. Many think that the position of a small effusion at the base of the chest is determined solely by gravity. This is not wholly true, as is demonstrated by experiment, for a relatively small effusion introduced into the pleural cavity of a dog will remain posteriorly between the lung and the diaphragm even when the board to which the dog is strapped is later inverted so that his body is vertical and his head down. Then the exudate will be found at the highest point of the chest. The explanation rests in the fact that the elastic recoil of the lungs maintains a negative pressure within the pleural cavity and supports the diaphragm, with the liver attached to it, against gravity. Over a liter of fluid must be introduced into the chest before it exerts a positive downward pressure on the diaphragm, that is, before the fluid will flow out if a hollow needle is plunged into the lower portion of a chest nearly half-full of fluid. On the contrary, under such conditions air would tend to rush into the chest. A small effusion will occupy a position and assume a shape within the pleural cavity both of which will be determined by the negative recoil of the lung. Its upper surface will by no means be flat. It will be bounded above by a surface of lung, every point of which is under equal tension. This is the reason why the fluid appears to be "fixed" by adhesions, i.e., does not move freely in the chest; it is also the reason why the movable line of dulness is so unsatisfactory a sign of fluid.

Palpation.—The early limitation of respiratory movements and the narrowing of the interspaces which occurs before much fluid has accumulated are due, as palpation would indicate, to increased spasticity of the intercostal muscles. Later on palpation frequently reveals better than inspection the following conditions: the distention of the affected side, the widening of the interspaces, the dislocation of the point of maximum impulses of the heart, etc.

Tactile fremitus will generally be absent over a large effusion and diminished over a smaller one. This is one of the most important of the physical signs. One of the best ways to estimate the upper level of the fluid is to determine the level where tactile fremitus ceases. In adults fremitus may persist if the pleural cavity has been obliterated in some measure by adhesions. Why the fremitus is obliterated is difficult to explain, since fluids conduct vibrations better than air. A reasonable explanation is that the vibrations created within the bronchi do not reach the surface of that part of the pleura which comes in contact with the fluid; that is, as the normal lung collapses because of the fluid its peripheral collapsed layer acts as a damper to the vibrations within. In pneumonia, on the other hand, the fremitus persists, since the consolidated masses containing the open bronchi transmit to the fluid the vibrations of the voice.

Palpation frequently shows that the temperature on the affected side is higher than on the other side, and may reveal a friction-rub early, while the effusion is collecting, or later, as it decreases in volume. On mensuration with a cyrtometer or a saddle-back tape the affected side is found to be larger than the other, the difference varying from one to one and a half inches (it should be remembered that the right side of a right-handed person is always a little larger than the left side).

Percussion.—The percussion-note over a very small effusion may at first appear to be normal, but as the volume of fluid increases the note becomes progressively impaired and, finally, even flat. On percussion the sense of resistance over the fluid is noted. This sensation is often of greater value in diagnosis than is the change in the percussion-note. Light percussion should be used. In cases of large effusion, that is, effusions which reach to the level of the fourth rib or above, the note over most of the fluid is impaired or flat, but just above this area of impaired resonance the note is high-pitched and tympanitic in quality ("skodaic resonance").

The lung is often spoken of as "compressed" above the fluid. This is usually incorrect. The normal lung is in a condition of constant inflation, since it is an elastic organ in a cavity which it must fill. Open the pleura of a healthy dog and stop the respiration, and the lung will collapse like a deflated balloon to about one-seventh of its former volume. Theoretically, therefore, this lung could not be compressed until it has collapsed to above one-seventh of its volume. But actually, the lung does not collapse uniformly like a rubber balloon. The lobe next to the fluid may be quite atelectatic, while the upper lobe is quite distended. In other words, the lobes, even part of a lobe, first collapse and make space for fluid while the rest of the lung remains almost normal. And, what is more, the air within the collapsed lung-tissue will in time be absorbed and thus make still more space for fluid.

Large effusions may reach as high as the clavicle in front and even beyond the sternum margin on the opposite side. In such cases the lung will lie posteriorly along the spine. The percussion note over these large effusions has a peculiar wooden quality, while the fingers get a definite feeling of resistance which is quite characteristic of pleural effusions.

The line of dulness of the upper level of a pleural effusion will not be horizontal but curved, unless the case is one of hydropneumothorax. Garland named this "Ellis' S-shaped line of dulness." To determine this, the examiner should have the patient sit erect, and should make a light percussion from above downward in a series of parallel vertical lines around the chest. The lowest point of this curved line will be at the spine. The line then curves upward and outward to the midscapula line, concavity upward; then it curves down across the axilla and proceeds in a straight oblique line down to the sternum. The value of this curve may be explained as follows: The fluid, when moderate in amount, is held up against gravity, while in the case of the larger effusions only the lower layers exert a positive pressure downward. Every point of the upper level of the fluid will be in static equilibrium. The pull of the lung at any given point of its surface will vary inversely with the amount of elastic lung between the hilum, the fixed point, and that point. Therefore, the level of the fluid will be lowest at the spine and highest in the posterior axilla.

Grocco's triangle, or the paravertebral triangle, is a triangular area of relative dulness on percussion at the spine at the base of the normal side. Its vertical side is the midline of the spine, its base a horizontal line at the pulmonary hepatic level extending from 2 to 5 cm. from the midline. This dulness on percussion is attributed to the fact that the fluid pushes the mediastinal structures across the midline. It is also held that the fluid itself forces its way between the lung and the spine and, therefore, acts as a damper. This triangle is determined by tapping the spine gently from above downward, to determine the apex of the triangle. The lower limit of pulmonary resonance is then outlined on the normal side. This will be the line of the base. The hypothenuse will be determined by percussing the chest gently from above downward in a series of lines parallel to the spine. The presence of this dull triangle practically always indicates fluid. It is not present in cases of solid tumor of the chest.

Traube's semilunar space, the space bounded by the lower margin of the left lung (the sixth interspace), the spleen (the midaxillary line) and the costal margin, normally tympanitic because of the stomach, is usually dull when there is free fluid in the left pleural cavity, and yet when the stomach is dilated it may be tympanitic.

The great importance of movable dulness in the diagnosis of fluid in the chest is often emphasized. The lower margin of pulmonary resonance in the mammary line is determined when the patient is recumbent and, again, when he is erect. The emphasis laid on this test is theoretical. The line ought to rise promptly several interspaces, but it never moves more than one space, and it does this so gradually that some assume that the fluid is not free in the chest, that is, is encapsulated by adhesion of the pleuræ. As a matter of fact, the free fluid in the chest is not free to seek its level as it does in hydropneumothorax. At this point it is only fair to ask whether or not the line of dulness which we determine is the actual upper level of the fluid. Skoda's rule for the height of the fluid in hydropneumothorax (double that indicated by percussion) does not fit simple pleurisy with effusion; and yet confidence that percussion alone will reveal the line where lung and fluid meet indicates that the results of percussion have not been properly compared with roentgenograms and with the results of exploratory punctures. To determine the height of the fluid light percussion should be made and the line obtained should be confirmed by testing the vocal fremitus and by auscultation with special reference to the voice and whispered fremitus.

Compensatory emphysema of the opposite chest may be demonstrated in rather chronic cases.

It should be borne in mind that the presence of a small effusion of about 400 c.c. in an adult cannot be detected by physical examination. Such an effusion will collect in the lower back and disturb the lower limit of pulmonary resonance very little. This is usually most noticeable anteriorly, a little in the axilla, and only slightly posteriorly. It may flatten the diaphragm only a little and cause practically no collapse of the lung. For this reason it has been suggested that the examination for fluid should be made with the patient resting horizontally on his back, with his hips on one bed and his shoulders suitably supported on another bed, and that the examiner crawl underneath and examine the back. The author has never tried this; he prefers the roentgenological methods.

Auscultation.—An audible friction-rub may be heard early, but this disappears as the effusion collects. In cases of small effusions this rub may continue above the level of the fluid. The disappearance of a friction-rub is due to the separation of the inflamed pleura and to the partial cessation of motion during respiration on the affected side. Its reappearance indicates the beginning of absorption of the fluid. The friction-rub is heard with inspiration and expiration, is close to the ear, is increased by pressure and is usually leathery and creaking in character. Care must be exercised to exclude the crepitation of a pneumonic lung; and yet this may be difficult, since in some cases of pleural effusion, in addition to the friction, a definite crepitation is heard, which is evidently pulmonary in origin but the cause of which is not clear. It may be due to the expansion and collapse during respiration of a slightly collapsed lung. While the reappearance of a friction-rub is usually evidence of improvement, it may, however, indicate an extension of the pleurisy to a previously unaffected area.

The breath sounds are faint over an exudate which is small in amount. These changes in the breath sounds are due partly to the diminished expansion of the partially collapsed lung, partly to limitation of motion on the affected side caused by nervous inhibition even in the absence of pain, but still more to the formation of a surface layer of collapsed lung-tissue which dampens the sounds produced within the bronchial tree. The breath sounds are faint, tubular in character, and expiration lasts a little longer than inspiration. As a lung collapses the breath sounds become more distinctly tubular. This is best heard in the scapular region above the level of the fluid. Sometimes only a puffing, tubular expiration is heard. These tubular sounds may be metallic or even amphoric. Sometimes one hears loud, resonant, metallic râles, which may suggest a cavity, the so-called pseudocavernous signs of an exudate. These are noted especially in children, in whom the breath sounds are also usually much more tubular than they are in adults. In the case of massive exudates the breath sounds may be low or entirely absent, or, again, they may be loud and tubular. Above the line of dulness the breath sounds are harsh and exaggerated, and, in this region, are often combined with a friction-rub. For a long time after the fluid has disappeared the breath sounds may remain faint. The author believes that these signs should be explained as follows: Even in the normal lung the peripheral zone of alveoli acts as a damper of sound, preventing the normally loud tubular respiration of the bronchial tree from reaching the surface of the lung. Only the vesicular sounds produced near the periphery are heard with the stethoscope, while louder, simultaneous sounds within the lung are not heard at all. That is the reason why it may be difficult to recognize a central pneumonia, and why large lesions near the hilum may give no physical signs. It is known that fluid is a fine conductor of sound, therefore, on the condition of the peripheral layer of the lung will depend the sounds which reach the ear through the fluid from the bronchial tree. If the lung is partly collapsed, some sound is heard; if it is atelectatic, more sound is heard.

Voice sounds are distinctly heard below the level of the fluid. This is always a valuable sign in determining its level. Whispered breath sounds are said to be transmitted through a serous fluid but not through pus (Bacelli's sign). This is not always (if often) true. Bacelli claimed that this sign should be tested by direct auscultation in the anterolateral portions of the chest. Bronchophony is usually present. By this is meant an intensification of vocal resonance. The whispered voice sounds are distinctly heard. Ægophony, that is, a curious nasal, bleating quality of sounds resembling those made by a goat, is rare. A suggestion of this is sometimes heard at the outer angle of the scapula and at the posterior inferior chest. Laennec laid emphasis on this sound and all subsequent students of physical diagnosis have tried to hear it. To hear the same sounds which Laennec heard and named is impossible unless one uses a stethoscope like his, a hollow, cylindrical wooden tube, over a foot long and above one and a half inches in diameter. Such an instrument with so large a resonance cavity would greatly modify sounds. Undoubtedly loyalty to Laennec causes the imagination to be stretched considerably by those who use his terms.

The coin sound is obtained in practically the same way as in pneumothorax, by placing a large coin flatly and firmly against the front of the chest and hitting this with the edge of another coin while the observer listens behind, below the level of the fluid.

The dislocation of the heart is one of the most important signs of pleurisy with effusion. This is definite in left-sided effusions of 700 c.c. or more volume and in right-sided effusions of 1,000 c.c. or more. The displacement will be less if pneumonia, emphysema or pleural adhesions are also present. The heart moves toward the normal side, still maintaining its normal direction and with very little swing (although it does swing a little in massive effusions). It is pushed to the normal side since the negative pressure on the side of the effusion has been lessened by the collapse of the lung which now has less volume to fill. Therefore, the greater pressure is on the side of the mediastinum where the effusion is, although this may still be below atmospheric pressure. The apex of the heart in cases of left-sided pleural effusion is located at the point where the heart sounds are most plainly heard. This may be under the sternum or in the upper epigastrium to the left of the ensiform. If the apex is behind the sternum, it may be that the impulse cannot be localized. Sometimes it is easier to feel the apex than to see it, although as a rule it is localized by auscultation. The point of maximum impulse, whether determined by palpation or by auscultation, may or may not be the apex-beat. This will depend not alone on the amount of fluid, but also on the part of the dislocated heart left exposed. For if the cardiac lapel of the left lung is retracted because of former pulmonary disease or old adhesions, the pulsation of the right ventricle may be conspicuous. Over the displaced heart a systolic blow is often heard. This is said to be due to the pressure of the fluid on the vessels of the mediastinum, especially on the pulmonic artery. In some cases in which pleurisy involves the cardiac lapel, a pleuropericardial friction is heard.

Greene [5] called attention to a rhythmical lateral displacement of the heart as a sign of unilateral pleurisy with effusion. This is best seen with the fluoroscope.

After the absorption of a long-standing pleural effusion begins, the heart may then be displaced too far toward the side of the effusion, since the negative pressure which sometimes develops on that side is greater than the normal.

The intra-pleural tension will still be negative in small effusions unless the case is complicated by some intra-pulmonary disease, or by adhesions. With an effusion less than one liter in amount, the pressure at the end of quiet expiration, when measured at the base of the chest, has been found to vary from 0 to +3 mm. Hg; with an effusion of from one to two liters, from +8 to +22 mm. Hg; and with an effusion of over +2 liters from +20 to +48 mm. Hg. The pressure may be even —40 mm. Hg at the end of deep inspiration in the case of small adhesions and even —90 mm. Hg after aspiration.

LABORATORY FINDINGS.—*Blood.*—The leukocyte counts in 89 cases varied greatly. In one case the count was above 15,000 per cu.mm., and in 26 cases (while there was a definite fever) it varied from 10,000 to

15,000. In 12 cases it was under 5,000. In a series of cases, all of which were possibly tuberculous, the count was found to be above 12,000 in 18.9 per cent. In those of this series which were positively tuberculous it was above 12,000 in 9 per cent.; in those cases of combined pulmonary tuberculosis and pleurisy with effusion it was above 12,000 in 21.8 per cent., while in those cases of pleurisy with effusion combined with pneumonia it was above 12,000 in 78.5 per cent. of the cases.

Urine.—During the development of effusion there may be a marked reduction of the output of urine, which is then concentrated and of high specific gravity. As the exudate absorbs, the output of urine increases and the chlorin output rises even to the point of a chlorin crisis. In some cases hematoporphyrin may be demonstrated in the urine of these patients.

Pleural Effusion.—In the typical cases of pleurisy with effusion (and such cases are usually tuberculous in character) the fluid is yellow or faintly greenish-yellow in color; it has a specific gravity of at least 1.018 and an albumin content of 4 per cent. or more. On the addition of acetic acid an abundant precipitate forms. The fluid contains much fibrogen and therefore coagulates rapidly, sometimes in small clots, while in other cases the entire mass of fluid clots to a gelatinous mass (in rare cases a little blood must be added to aid clotting). Microscopically it contains leukocytes and a few red blood-cells. In the majority of cases most of the leukocytes are small mononuclears.

Diagnosis of the etiology of an effusion based on the formula of its cell-count (cytodiagnosis) has attracted much attention. The fluid to be examined should be received into a sterile flask about one-third full of 0.85 per cent. sodium chlorid solution and containing also 1 per cent. sodium citrate. This fluid is centrifugalized and smears are made from the sediment and stained in the same manner as are blood-smears. The following leukocytes can be recognized in these smears: small mononuclears, polymorphonuclear finely granular cells, polymorphonuclear coarsely granular cells, basophils and endothelial cells. The latter demand special attention. Some may be the large mononuclear leukocytes of the blood (the so-called endothelial leukocytes), while others occur in sheets as though stripped directly from the pleural membrane. Some are phagocytic. All of these leukocytes are apt to have pyknotic nuclei and vacuolated, degenerated protoplasm. Widal claims that if the majority of the cells in an exudate are finely granular the case is one of pyogenic infection; in cases of tuberculous pleurisy the small mononuclears will predominate, while in those of mechanical origin, the endothelial leukocytes will predominate. But the formula varies not only with the etiology but with the intensity of the infection and with the duration of the effusion. The formula therefore is only suggestive. There may be a transitory leukocytosis in cases of early tuberculous pleurisy; in such a case there may also be a secondary infection of the pleura with pyogenic organisms. Many effusions which are clearly nontuberculous in character may later have a preponderance of small round cells in the fluid. In fluids due to mechanical causes the relative excesses of endothelial cells is early and transitory. Later the small mononuclears may predominate. The polymorphonuclear finely granular cells seem least subject to variation. Some cases with pleural effusion, in which the small mononuclear leukocytes were clearly in predominance, are found at autopsy to be definitely non-tuberculous. In cases of malignant disease involving the pleura the fluid may at first resemble that due to mechanical causes, but in other cases the mulberry-like masses of proliferated endothelial cells (proliferative pleurisy) and the cells showing mitotic figures may aid in the diagnosis, while in some cases of sarcoma involving the pleura the numbers of spindle-shaped cells may suggest the cause. Lord, in 28 cases of pleurisy with effusion, found that the small mononuclears composed from 90 to 100 per cent. in 24 cases; 88 per cent. in 1; and from 70 to 75 per cent. in 3 cases. In the last 3 cases the epithelial leukocytes and the coarsely granular cells predominated. If the pleurisy with effusion is complicated by pulmonary tuberculosis, there may be a mixed infection and therefore a larger number than usual of polymorphonuclear cells present. In chronic passive congestion, also, there is a lymphocytosis; therefore, a predominance of these cells does not always indicate tuberculosis, although it nearly always does. In cases of non-tuberculous pleurisy with effusion the polymorphonuclear neutrophils may be in excess; in some, the small mononuclears predominate. The small mononuclears may also predominate in a mild pyogenic infection which is subsiding. In transudates the epithelial cells are in the majority, but, if the fluid is of long standing, the small mononuclears predominate. Secondary infection may confuse the picture. The fluid may also contain red blood-cells. Cholesterin, uric acid and sometimes sugar are also found. In its chemistry the fluid resembles blood-plasma. The proteids are serum-albumin, serum-globulin, nucleoalbumin and fibrinogen. The albumin will amount to 4 per cent or over. The fluid may coagulate spontaneously. Recently the predominance of eosinophil cells has attracted some attention. Bine[6] reported 2 cases of atypical pulmonary infection followed by pleural effusion. In one case the blood contained 1 per cent. and the pleural effusion 51 per cent. of eosinophils. Four years later, after the effusion had disappeared, the coarsely granular cells of the blood numbered 32 per cent. In the second case these cells numbered 16 per cent. in the blood and from 30 to 40 per cent. in the pleural effusion. Bine's conclusion is that an eosinophilia of the pleural effusion precedes that of the blood, reaches a higher point than in the blood, and is the first to disappear. The etiology of the cases with pleural eosinophilia is so varied that this formula can have little importance in diagnosis. The condition has been found following trauma and in typhoid fever, pneumonia, tuberculosis, syphilis, polyarthritis, general sepsis, pulmonary gangrene, endothelioma, hemorrhagic infarct of the lung, cardiac insufficiency, influenza, etc. A pleural eosinophilia and basophilia not infrequently develops in cases of traumatic hemothorax. In some cases the eosinophils number from 60 to 75 per cent. of the total cell-count. They seem to be formed locally in the pleura and to be the result of a special degeneration of leukocytic elements which can occur only in an aseptic medium. These cells later reach the blood and cause a tardy eosinophilia. Petzetakis[7] believed that they are formed directly from the polynuclear finely granular leukocytes.

Bacteriological Findings.—The pathogenic organisms in pleural exudates may, if present, be demonstrated in cultures or even in smears made directly from the fluid as it is removed. The demonstration of *Bacillus tuberculosis*, however, is exceedingly unsatisfactory because of the very small number of these organisms in the large volumes of the fluid. (*See* page 594.) Jousett's method of inoscopy has been much used. At least 100 c.c. of the fluid are allowed to clot; the clot is then washed in sterile water with sterile gauze and transferred to a flask. To this is added from 10 to 30 c.c. of a digestive fluid consisting of pepsin, from 1 to 2 grams (15.43 to 30.86 grains); pure glycerin and concentrated hydrochloric acid, 10 c.c. (2.71 fluid drams) each; sodium fluorid, 3 grams (46.30 grains) and enough distilled water to make 1,000 grams. This mass is digested in the thermostat at 38° C. (100.4° F.) until the clot has disappeared; this usually requires from two to three hours, but this time may be shortened by occasionally shaking the mixture. The fluid is then decanted and smears are made from the sediment. Zebrowski recommends that 100 c.c. or more of the fluid be mixed with an equal amount of 1 per cent. sodium fluorid solution and kept in a cool place for twenty-four hours and then decanted. The sediment is then centrifugalized and smears are made. Animal inoculation is, however, the only certain way of determining the presence of these bacilli. To be accurate, a large amount of the fluid must be injected into the peritoneal cavity of a guinea pig. According to some from 10 to 50 c.c. are injected each week until at least 300 c.c. have been introduced. The amount possible to inject will depend somewhat on its toxicity. The animal is then allowed to live for three months (unless it dies before then, in which case, of course, it is immediately autopsied). At the end of this time the animal is killed and examined. Using this method *Bacillus tuberculosis* has been demonstrated in 85 per cent of the cases of pleurisy with effusion. (Le Damary claims to have demonstrated it in 93 per cent. of his cases.)

Roentgenological Findings.—The *x*-ray examination of the chest is of greatest value in the diagnosis of pleurisy with effusion. In the case of small effusions this is often the only way in which a diagnosis can be made. The fluid may present a vertical column along the spine at the base of the chest and move very little on motion, since it is held there by the elastic lung. The dark shadow with concave upper surface, the highest point against the chest-wall, is pathognomonic of a small effusion. The *x*-ray plates are very valuable in showing the coëxistence of a bronchopneumonia with pleurisy, or the position of an encapsulated effusion. It is said that the shadow of a serous effusion is less dense than is that of blood or pus.

Diagnosis.—In a case of suspected pleurisy with effusion two questions arise: First, is there fluid in the pleural cavity? Second, if there is, what is the character of the fluid? Serous, serofibrinous, hemorrhagic, fibrinopurulent, purulent, chylous and chyliform fluids are to be considered. In general it may be said that, in an acute case, dulness in the lower back, with loss or reduction of fremitus and without the cough and sputum indicating pneumonia, suggests the probable presence of fluid. If the dulness extends into the axilla, there is much better basis for this suspicion, and exploratory puncture should be made.

One of the most important conditions to exclude is *pneumonia,* especially of the massive variety. The note on percussion over an area of pneumonia will be very dull, but perhaps not quite so flat as that over fluid. While in ordinary lobar pneumonia there will usually be definite bronchitis, with cough and rusty sputum, increased tactile fremitus, and, on auscultation, definite tubular breathing, yet in massive pneumonia there may be a diminution of tactile fremitus similar to the diminution over fluid. In pneumonia the onset of the illness is generally much more abrupt than it is in pleurisy, the chill is more severe, the temperature curve higher, the dyspnea greater, the cough a more conspicuous feature, and the sputum definitely blood-streaked or rusty. In pleurisy with effusion there may be a very acute onset with all the physical signs of acute lobar pneumonia, but no cough or sputum whatever may be noticeable. In cases suggesting lobar pneumonia, but presenting no cough and sputum, it is best at first to make a careful examination for other possibilities. In pneumonia there may be a slight apparent increase in the size of the chest with immobility on respiration and yet the organs of the mediastinum are usually not displaced. Since pneumonia and a pleural exudate are often combined and since also such an exudate is often a sequela of a pneumonia, it is well in every case of acute lobar pneumonia to make accurate record of the point of maximum impulse of the heart, for the dislocation of this may be the first accurate evidence of an effusion. The note on percussion over fluid is apt to be more wood-like in quality, and the resistance felt by the fingers more definite than it is over a consolidated lung. The intercostal spaces will be more definitely obliterated by fluid. On the other hand, the tubular breath sounds in some cases of pleurisy with effusion may be very high-pitched and even amphoric, and so may be very deceptive. It is well to bear in mind that in certain atypical pneumonias there may be no cough and no sputum, and that on exploratory puncture in pneumonia only a little fluid can be obtained. In any pneumonia it is well to be on one's guard in case there is a delayed crisis or a long-continued lysis, a recrudescence of the fever, chills and sweating, a persistent leukocytosis or the appearance of a paroxysmal cough; for these conditions often mark the beginning of an effusion which is sometimes, though rarely, serous in character.

Marked chronic suppurative changes in the lung, associated with *multiple bronchiectatic cavities, interstitial pneumonia,* thickened pleura and plugged bronchi, must be excluded. In these cases there is not the uniform dulness on percussion found in pneumonia or in cases with effusion. The heart will be in a normal position, the diaphragm will be elevated rather than depressed, and the chest will be contracted.

In cases of *hydrothorax* accompanying general anasarca the clinical history is quite different. There will be no history of onset suggesting an acute infection (e.g., pain, pleurisy and fever), but rather a history of preceding cardiac or renal disease, or both. Furthermore, the fluid accumulates slowly and is more apt to be bilateral. There will also be at least a little edema elsewhere over the body. The fluid on aspiration in hydrothorax will be found to have a low specific gravity, 1.010 or less, albumin about 1 per cent., and it will not coagulate spontaneously. In cases of hydrothorax due to venous stasis from heart disease, the specific gravity of the fluid will vary from 1.010 to 1,018, the albumin will be about 3 per cent., a slight precipitate will form on the addition of acetic acid, and slight spontaneous coagulation will be noticed. (Usually a little blood must be added to supply sufficient fibrinogen.)

In cases of *hemothorax* there will usually be the history of trauma or the evidence of malignant disease. Hemothorax may be suspected if the circulating blood shows a definite eosinophilia.

In *chylothorax* the same fluid will generally be found in the abdomen.

Empyemas are more often secondary infections. This is especially true of the metapneumonic type. The fluid in the chest of children under five years of age is generally purulent. In empyema the symptoms are more severe, the temperature is higher and more irregular, the loss of weight and strength is greater, and a more rapidly developing secondary anemia and usually a leukocytosis of over 12,000 are present. Chills and sweating are more common. There is usually dilatation of the superficial veins, and pulsation, or even perforation, of the chest-wall is apt to follow. A marked secondary anemia is not always a reliable sign of pus since it may develop to a marked grade in children with serous effusions, or in adults with long-standing clear effusions, while in acute cases of empyema there may be no noticeable anemia.

Pericarditis with effusion must be differentiated from pleural effusion on the left side. In the former there is usually a history of rheumatism; the patient presents more cyanosis than in the latter, and a dyspnea which is more urgent than the apparent amount of fluid would indicate. The cases with pericarditis have greater dilatation of the cervical veins than the latter, and pulsus paradoxus may be demonstrated. In the former, also, an oval or pear-shaped area of dulness, reaching as high on the left as the second rib, is found on percussion and there is dulness in the left infrascapular region. A pericardial friction-rub is usually present. Over the base of the chest there will be resonance which extends toward the axilla (skodaic tympany). The point of maximum cardiac impulse (determined by auscultation inasmuch as it cannot usually be felt) will not be dislocated to the right, and the heart sounds will be faint. The lines of the right border of cardiac dulness and of the pulmonary hepatic line of dulness will meet at an obtuse angle. The x-ray plates will give valuable evidence.

A *thickened pleura* may be excluded by the note on percussion, which will be dull, but less flat than when made over fluid, by the breath sounds, which will be faint with expiration prolonged, but not definitely tubular, and by the vocal fremitus which is often diminished, but sometimes increased. Grocco's triangle is absent and the heart will not be displaced. On exploratory puncture the thickened tissue through which the needle passes can be felt, and a dry tap will be obtained.

Intrathoracic *tumors* and *cysts* involving the pleura must be excluded. This may be difficult, since some, especially the hydatid cysts, are often accompanied by an effusion. In all such cases the area of dulness will have neither the position nor the shape of that due to free fluid and Grocco's triangle will be absent. There will be no fever, and often there will be bloody sputum, dyspnea, stridor, dilated pupils, dysphagia and dilatation of the vessels of the neck. In any long-standing case of apparently large effusion without cough or expectoration but with localized points of pain constant in position, an intrapleural tumor should be suspected. The fluid in the pleura in tumor cases is often bloody and rich in tissue-cells. It may even be possible to obtain a small amount of the tissue from the lumen of the needle used for puncture. Abscess of the liver must sometimes be excluded, as well as a subdiaphragmatic abscess or tumor. In these cases there is no cough or sputum indicating lung involvement, and probably there is no history of previous abdominal trouble. The right side is more apt to be involved. The elevated dome of the diaphragm can be outlined on percussion, but there will be no flat note suggesting fluid, no egophony and little displacement of the heart, while the x-ray plates will give valuable evidence. A friction sound is frequently heard over the dull area in cases of abscess.

Cancers of the kidney, especially those which grow upward and involve the diaphragm early, will sometimes be confusing, for these are often accompanied by a pleural effusion.

Exploratory puncture should be employed freely in any case in which fluid in the pleural cavity is suspected, especially if a satisfactory roentgenological examination is not possible. It is far better to puncture unnecessarily than to overlook an effusion. The sterilized skin should be frozen with **ethyl chlorid**, or anesthetized with **novocain**. A long, stout needle with a diameter of at least two millimeters is inserted along the upper margin of a rib so that intercostal arteries are avoided. In some cases the pus is so thick that it will not follow readily through a needle, even of this size. In the case of encapsulated mural or interlobular abscesses, or of the diaphragmatic form of encapsulated empyema, it may be necessary to explore by operation in order to find the fluid, although with the use of the x-ray it can usually be located in advance.

Complications.—Pulmonary tuberculosis is the most dangerous complication of pleurisy with effusion. The disease may extend from the pleura to the lung or from the lung to the pleura. Acute miliary tuberculosis rarely develops.

The extension of the inflammatory process to the other pleura or to the pericardium is important, while perihepatitis and perisplenitis are not rare complications. Thrombosis of the pulmonary vessels and of the peripheral veins is common. The latter often results in embolus. Edema of the lung is a dangerous complication in the case of large effusions, especially if they are allowed to remain untapped for a long time, or if cardiac weakness from any cause develops. Sometimes these effusions perforate through the lung and occasionally through the chest-wall, but this occurs much less often than in the case of purulent effusions. Serous expectoration, especially after paracentesis, is an important complication.

Sequelæ.—Chronic pleurisy with effusion may last for months and even for years, if the condition is untreated. About 1 per cent. of the cases are very chronic and have an average duration of over two years. Chronic dry pleurisy is a not uncommon sequela. The formation of layers of firm connective tissue which is thickest at the base will result from the organization of the layers of fibrin which were deposited on the pleura during the acute process. The result will be a contracted chest (which, however, occurs less often and in less severe grades than after empyema) with scoliosis of the spine, dragging pain and an occasional stitch in the side, which may last for years, although some patients with contracted chests have very little trouble. Sometimes a pocket of fluid remains between the layers of the thickened pleura as a pleural cyst.

Pulmonary fibrosis may follow long compression of the lung, or long-continued adhesion of the collapsed lung to the chest-wall. It may be the result of the direct extension of scar-tissue formation from the thickened pleura.

A serous fluid rarely becomes purulent. This condition was found in only 1.3 per cent. of 1,185 cases. When this happens spontaneously, it is likely that from the first the fluid, while apparently serous, contained an excess of finely granular leukocytes. Although some truly serous effusions become infected from the lung, yet the infection is mostly due to an error in the technic of tapping. Pneumothorax, also, may result in this manner.

The heart may be held permanently in its dislocated position by pleural adhesions which developed during the period of the effusion.

Clinical Varieties.—Several clinical varieties of pleurisy with effusion differentiated chiefly by their etiology have been noted in the preceding pages. In addition pleuritis acutissima may be mentioned. These cases, which are few in number, begin with a severe chill followed by a rapid rise of temperature. They are characterized by the rapid accumulation of a massive effusion causing intense dyspnea and cyanosis. The pulse and respiration become progressively more rapid. Unless the condition is relieved at once such a patient will become delirious and will die in a few hours.

French writers mention a type of pleurisy with effusion common among farm workers. The effusion occurs in the upper front of the pleural cavity, which localization is explained by the occupation of the patients.

Treatment.—GENERAL MEASURES.—In the treatment of pleurisy with effusion it is wise to assume that every case is one of tuberculosis unless proven otherwise. That is, treatment must be planned for the pleurisy and also for the latent but active tuberculosis of the lymph-glands, or lungs, or both. As long as fever is present the patient should **rest** quietly in a warm and comfortable bed placed in the open air and sunshine. The **climate** is as important in the treatment of pleurisy as it is in pulmonary tuberculosis; therefore, the patient should reside where he can be out of doors as much of the time as possible. A sleeping-porch is almost a necessity. A dry **diet** is suggested by some, although with little reason, since there is no evidence that the amount of the inflammatory exudate bears any direct relationship to the amount of water ingested. The diet for pulmonary tuberculosis is better; it consists chiefly of milk, cream, and eggs, cod-liver oil, etc.

LOCAL TREATMENT.—The severe pain at the onset is to be treated like that of acute fibrinous pleurisy. It has been the custom in past years to **bind the affected side** as tightly as possible. This may be a mistake, since the binder may aid in the dislocation of the organs, and it may also hinder the absorption of the fluid. Cupping, both wet and dry, was formerly popular. The dry cups are not desirable because they may infect the field of a possible operation. The same objection applies to blistering, which does, however, relieve the pain. Nevertheless, **counter-irritation** is valuable. Light application of a **cautery**, or of a lighted **electric bulb**, the use of a **mustard plaster** or an abundant application of **tincture of iodin** may bring relief if applied over the chest.

MEDICAL TREATMENT.—Medicinal treatment has little value other than to relieve certain symptoms. **Morphin, Dover's powder** at night, etc., are useful. **Salicylic acid** or the **salicylates, diuretin,** and **iodin** in large amounts have been used. **Digitalis** should be used freely if it is needed. **Saline purges** which cause copious watery stools may be of assistance. Repeated intravenous injections of **hexamethylenamin** is advocated by some, but their published results are not much better than those obtained by the expectant treatment. **Cod-liver oil** is a medicinal food of great value.

ASPIRATION.—It may be stated that in pleurisy with effusion the fluid should generally be removed as early and as completely as possible and that the tapping should be repeated as frequently as necessary. This is a truly American treatment first recommended by Wyman and Bowditch. If the fluid found on exploratory puncture is clear, simple aspiration is sufficient; if it is purulent, then a rib should be resected and free drainage maintained; but if it is slightly turbid, then the method used will depend upon the organisms found in smears. If the pneumococcus is found, and especially if the patient is a child, aspiration is to be resorted to; but if the streptococcus is found operation is indicated unless a pneumonia is then in progress.

Delafield reported 200 cases of serous pleurisy treated early by aspiration with excellent results. He says that his method not only hastens recovery, but that it also prevents the formation of adhesions, of thrombi and of pulmonary infection. Fever is not a contra-indication to aspiration. Lord classifies the indications for tapping as follows: an effusion large enough to cause definite dislocation of the heart, even though there is no dyspnea; a fluid, moderate in amount, which in two or three weeks presents no change in volume; the presence of cyanosis of dyspnea or of cardiac weakness; and lastly, a bilateral effusion. Others recommend that aspiration be delayed until there is assurance that the fluid has ceased to increase in amount (unless it has already reached a dangerous volume). In a case with moderate effusion and without adhesions it is best to introduce the needle either at the fifth or sixth interspace in the midaxilla, while the arm on that side is raised so that the hand is on the head, or at the seventh or eighth interspace in the posterior axillary line; in this case the hand on the affected side should be placed on the opposite shoulder. In the latter case the patient cannot see the needle. If old pleural adhesions are suspected, a spot where vocal fremitus can be felt should be avoided. If the fluid stops flowing suddenly before the signs indicate that the chest is well emptied, it is well to introduce the needle at another point. Whatever method of aspiration is used, the fluid should be withdrawn slowly; even half an hour may not be too long a period to consume in emptying the chest. A trocar provided with a side valve and stilette is safer than a sharp needle. It should be at least 7 cm. long, and should have a bore of from 1½ to 2 mm. in diameter. As a rule Potain's aspirator is employed; this consists of a bottle of at least one liter capacity which is closed with a rubber stopper perforated by two tubes, each of which is fitted with a good stopcock. One tube is connected with the trocar, the other with a suction pump. A partial vacuum is first created in the bottle, the trocar is introduced, and the valve is opened which connects the trocar and the bottle. However, a dangerously high negative pressure can be created with this pump. Other authorities prefer siphonage. In this process a rubber tube long enough to reach from the patient's bed to the floor is attached to the trocar. This is filled with sterile water in order to prevent the aspiration of air, and the free end is kept under the water in a basin resting on the floor. Opinions differ as to the amount of fluid which should be withdrawn. It is not necessary to quite empty the chest, since a certain amount of fluid will be easily absorbed. Most authorities insist that not over one liter should be removed at any one time. If much is left, the aspiration may soon be repeated. On the second aspiration more fluid may safely be removed than on the first, granting that the former attempt was satisfactory. This is evidence of the importance of the mental attitude in the causation of symptoms. Less should be removed from a long-continued effusion than from a more acute one. If the lung is known to be the seat of active tuberculosis not very much fluid should be removed. Sudden death has been the penalty of the too rapid evacuation of a pleural effusion.

The accidents of aspiration, which are also the indications for stopping, are severe pain, severe paroxysmal cough, bloody expectoration and evidence of collapse. Pneumothorax sometimes follows aspiration in case the visceral pleura is torn, or if, as has happened, the pump is wrongly adjusted to the bottle, and a positive air pressure, rather than a vacuum, is created within the bottle. Subcutaneous emphysema may result from puncture of the lung. In such cases the lung becomes glued to the chest-wall and the air within the smaller bronchi is pumped into the subcutaneous tissues by respiration and coughing. A condition of faintness is not uncommon and is usually psychical in origin. Epileptic convulsions have occurred during the withdrawal of fluid, while hemiplegia and sudden death have also been reported. After successful aspiration some cases present symptoms suggesting serum illness, due, it is supposed, to the rapid absorption of the fluid remaining in the chest. These symptoms are pain in the joints, albuminuria and edema. Albuminous expectoration, sometimes fatal, has followed aspiration, in which case it is believed that the fluid was removed too completely or too rapidly. Several protests have recently been made against too complete aspiration. Panto suggested that from 80 to 100 c.c. of fluid be aspirated on alternating days three or four times; he advises that the needle should be inserted at a different place each time. This treatment is based upon the theory that the mechanical irritation of the chest by repeated small tappings is important. It is claimed that in cases thus treated all of the fluid will disappear in from ten to fifteen days. Maurizi of Milan avoids aspirating in tuberculous cases, unless the fluid is considerable in amount, but he injects into the pleural cavity a suspension of from 2 to 4 grams (32.4 to 64.8 minims) of liquid petrolatum.

SERUM TREATMENT. — The value of autoserotherapy (Gilbert's method) has been widely acclaimed. According to this method one removes a few cubic centimeters of fluid from the pleural cavity and then at once injects the same into the subcutaneous tissues of the patient. This is supposed to stimulate rapid absorption. Remarkable results were at first claimed for this treatment. Lyter[8] has studied this method carefully, and has decided that it has very little value. Of 23 cases of tuberculous pleurisy treated in this way, 8 spontaneously absorbed the fluid in two weeks. This is approximately the number that would have absorbed the fluid in that time had no special therapy been used.

The after-care of these cases is particularly important, since each may be suspected of being a case of tuberculosis of other organs and should be treated accordingly.

Since there is likely to be a certain amount of contraction of the chest due to the thickening of the pleura, it is wise during convalescence to employ the *pulmonary gymnastics*.

Prognosis.—The immediate prognosis of a case of pleurisy with effusion is good, for these cases tend to spontaneous cure. It is remarkable how little disturbed these patients may be, even though one pleural sac is full of fluid and the heart quite dislocated; and yet in each case there is certainly some risk, due to the presence of the fluid. Of 320 cases at the St. Bartholomew Hospital, 6.1 per cent. died while in the hospital. Of 500 cases collected by Lord, only 0.8 per cent., or 4, died from the effusion; or, rather, this was the only apparent cause of their death. One of these patients died of pleuritis acutissima; of 2 with double effusion which had not been tapped, one died of pulmonary embolus and one of edema of the lungs, while the fourth, with single effusion, died of pulmonary embolus.

After post-traumatic pleurisy the chest seems to recover entirely, while a spontaneous effusion usually leaves traces behind (adhesions, thickened pleura, etc.).

The general statement is often made that in 80 per cent. of the tuberculous cases the effusion will absorb without aspiration. This may be true, and yet the ultimate prognosis certainly is made worse by such expectant treatment, since the effusion in many cases will remain for months, and the progress of the tuberculosis elsewhere in the body will not be checked as easily as if the patient were spared this long illness.

The rapidity of absorption of an exudate will depend to a large degree upon the condition of the surface of the pleura, for, if this is covered by an extensive and thick fibrin layer, there may be practically no absorption. The absorption will also depend upon the size of the effusion, the general health of the patient, the complications (e.g., cardiac disease) and upon the date of the first tapping. The younger and stronger the patient and the earlier the first aspiration, the more rapidly will the fluid absorb.

Pleurisy with effusion seldom recurs in the same patient, possibly because the first attack in a measure obliterates the pleural cavity.

As may be expected, there are those who defend the effusion and condemn aspiration. They claim that the formation of the exudate is a protective measure, that the fluid neutralized the toxins, or that it may contain protective substance, and that it mechanically forces the lung to rest (as does the air in artificial pneumothorax). It is more than possible that the pendulum will swing to an attitude of still greater respect for these "beneficent secondary pleurisies with effusion in cases of pulmonary tuberculosis."

Sudden death, which occurs especially in connection with large left-sided effusions, may be due to the disease producing the pleurisy, to a complicating disease, to a sudden change of posture, to paroxysms of cough, to thrombus and embolus, especially of pulmonary vessels (the most common cause), to cerebral embolus, to edema of the lungs, and to cerebral anemia. It is also claimed that it may be due to kinking or pressing on the vena cava.

It is said that at least from 30 to 40 per cent. of the cases of pleurisy with effusion will develop definite pulmonary tuberculosis in from six to twelve years.

Pathology.—The fluid will generally be found at autopsy at the base of the chest. It is not as often encapsulated as are purulent exudates. If encapsulated, the pocket is usually in the posterior inferior part of the chest. In a few cases the fluid will be in two pockets, and in rare cases one of these pockets will contain a serous fluid and the other pus. The left side is more often affected than the right (left, 52 per cent., right, 45 per cent., and bilateral, 3 per cent.). If judgment is based on the fluid it is sometimes difficult, at autopsy, to exclude transudates, because circulatory failure develops just before death; however, the examination of the pleura will decide this.

The amount of fluid present in the chest will vary from ½ to 4 liters. The amount of fibrin in the fluid will vary considerably. In some cases there is only a trifle, while in others the pleural surfaces are coated by a creamy layer of fibrin from which streamers float out into the fluid, while a wet, curdy mass of fibrin covers the base of the chest. At autopsy the fluid varies in color from a lemon shade to a dark brown or even a chocolate, if blood is present. It is usually clear or slightly turbid, the turbidity being due to flocculi of fibrin and to fat droplets. At autopsy most of the cells will be found to have settled at the base of the chest.

The pleural surface usually looks very much as it does in fibrinous pleurisy. In cases of tuberculous pleurisy tubercles may be macroscopically seen in the pleura; in other cases they may be seen only in microscopical preparations. One can easily separate the layers above the level of the fluid in the acute cases; however, in some chronic cases there will be adhesive pleurisy above, and bands of adhesions will pass through the fluid. In such cases the fluid is tightly enclosed in pockets by the firm union of the pleural surfaces surrounding it.

In cases of large effusion the lung will be found compressed along the spine in the upper, posterior part of the thorax. It may be airless, tough and leathery, dark in color and apparently bloodless (carnified). In cases of small effusion the lower lobe may be atelectatic while the upper lobe is slightly emphysematous. The lung on the normal side will, in long-standing cases, often show a slight compensatory emphysema. The liver is low, not because of the direct pressure of the fluid, but because of the diminution of the negative pressure which normally holds the liver up into the thorax even against gravity.

The heart is dislocated toward the nórmal side. The heart is not twisted, but the whole mediastinum is moved bodily. The point of maximum cardiac impulse has never been found to the right of the midsternal line. The apex is often slightly lifted so that the heart is more horizontal than normal. The diaphragm is flattened.

EMPYEMA

Definition.—Empyema of the chest is pleurisy with purulent effusion, that is, with an effusion definitely cloudy because of the presence of abundant polymorphonuclear, finely-granulated cells, and, in rare cases, of coarsely granular cells. The term empyema might be used of a collection of pus in any cavity of the body, but usage has practically limited this term, when the cavity is not specified, to pus in the chest.

The common and apparently primary pneumococcus empyema will be described below first. A second group will include the cases clearly secondary to some other disease, such as pulmonary tuberculosis or acute lobar pneumonia. A third group will embrace the cases in which the empyema follows a serofibrinous pleurisy, and a fourth group will consist of the cases which follow accident or which are secondary to any pyogenic infection of the body.

Etiology.—Of the pneumococcus empyemas, the great majority occur during the convalescence of a croupous pneumonia. The pneumococcus causes from about 50 to 60 per cent. of all cases of empyema. In the case of children the percentage is still larger. The streptococcus empyemas, which prior to the epidemic of 1918-19 were about 25 per cent. of all, are in nearly all cases preceded by a *bronchopneumonia* which may be demonstrated by physical signs, by *x*-ray, or at autopsy. Cases of *Streptococcus hemolyticus* empyema without a preceding bronchopneumonia have been reported and possibly occur, but the more carefully the cases are studied, the more it is evident that most of them are due to a latent bronchopneumonia. Most of the streptococcus empyemas are due to direct extension of the infection through the pleura by way of the lymphatics. Many are preceded by the formation of a small abscess underneath the pleura. While, in the pneumococcus type, the empyemas develop late in the course of the pneumonia, the streptococcus empyemas develop early, and clinically it would seem as though their frequency bore a direct relationship to the severity of the pneumonia, which may, however, be very limited in extent.

A common form of empyema is associated with *tuberculosis.* A pure tuberculous empyema has been doubted by some who claim that these cases are probably always due to a mixed infection. Cultures of the fluid, however, are usually sterile and therefore suggest tuberculous origin, and yet some say that even in these cases a streptococcus caused the empyema and later died out.

Empyema may follow scarlet fever, measles, influenza especially, typhoid fever, tonsillitis, and practically all *infectious diseases.* It may be due to perforating *wounds* of the chest and to disease of the mediastinum or abdomen, and especially to *disease of the liver.*

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The onset in a typical case of empyema is often abrupt and similar to that of pleurisy with effusion, which it resembles during the course except that the symptoms in empyema are usually a little more severe. The pains at onset are often stabbing, while in some cases they are general. In other cases, however, there is no pain, and little or no cough.

Course of Disease.—Dyspnea does not appear until the chest becomes quite full of pus or until the patient happens to exert himself to an unusual degree. These primary cases with insidious onset are even more numerous than the more "typical" ones which begin abruptly. The cases of the second group which develop in the course of another disease are more often very insidious in their onset. In the third group the fluid is clear at first, although the differential count of the cells in this fluid will generally show a predominance of polymorphonuclear cells. It then becomes more and more cloudy, and the symptoms resemble more and more those of a septic infection. The onset in the fourth group is masked by the symptoms of the antecedent diseases, those of empyema merely adding themselves to those of the general infection.

The general symptoms of empyema are those of any septic infection: gradually developing pallor with weakness, sweats and irregular fever, loss of weight, malaise, slight jaundice and anemia.

Those cases which follow or complicate acute lobar pneumonia begin insidiously during defervescence or after a brief period of apyrexia; in other cases of pneumonia, and especially those complicating streptococcus bronchopneumonia, the empyema develops rapidly at the height of the disease, even on the fourth or fifth day of the illness.

Objective Symptoms.—The objective symptoms of empyema, when the disease is at its height, are cough, usually dry, but sometimes with a slight mucous sputum which is by no means constant; dyspnea on exertion; sometimes orthopnea; and marked pallor combined with secondary anemia. The affected side of the chest appears distinctly larger than it does in serofibrinous pleurisy. The intercostal spaces may even bulge. This is especially true in children. This condition is said to be due to the greater weight of the fluid. However, the author believes one important cause to be that the severe infection disturbs more profoundly the mechanism of respiration. Often there is edema of the chest-wall and distention of the subcutaneous veins on the affected side. The diminished pulmonary excursion is important in diagnosis. The displacement of the heart and of the liver are more marked than in serofibrinous pleurisy. Grocco's triangle is not of very great value. In some cases a distinct pulsation of the chest-wall over the fluid is seen, synchronous with the heart-beat (pulsating pleurisy). In some cases there is distinct bulging of the chest at one point over the effusion (empyema necessitatis). This tumor may pulsate. In chronic cases the fingers may become definitely clubbed (Hippocratic fingers). This condition may develop rapidly in two or three weeks and disappear soon after the evacuation of the pus.

PHYSICAL FINDINGS.—*Palpation.*—Tenderness on pressure and on percussion is usually marked over an empyema. This is a valuable aid in determining the point at which the needle should be inserted for exploratory puncture. On palpation some edema of the chest-wall is often detected.

Abdominal distention and rigidity are common and important signs. The diagnosis of an acute abdominal infection with peritonitis is sometimes made. The absence of vomiting is an important point in diagnosis. The abdominal signs are usually unilateral and indicate the involvement of the diaphragm. Head's zone of hyperesthesia can usually be demonstrated. In the pneumococcus empyemas the tactile fremitus is usually lost, a valuable sign in differentiating this disease from lobar pneumonia; yet in streptococcus empyema the fremitus is often distinctly felt even though considerable fluid is present. Probably in the former condition the lung is collapsed and almost airless, while in streptococcus cases, with distinct fremitus, the lung is still distended by areas of bronchopneumonia, and therefore is capable of transmitting vibrations within the bronchi to the fluid. The liver is usually lower than in cases with serous effusion.

Percussion.—The altered percussion note is the most constant and valuable sign of fluid in the chest. As a rule the note will be flat over the fluid. In other cases, however, skodaic resonance can be distinguished even over a large quantity of fluid, due, some say, to the fact that the lungs are not collapsed, or that the pleura is not thickened.

Auscultation.—The physical signs on auscultation are practically the same as those of pleurisy with effusion, but in children the breath sounds are more apt to be loud and tubular, while in an adult, as a rule, they are faint or absent. The breath sounds and the voice fremitus are sometimes transmitted through a massive fluid with great distinctness, although this is seldom the cause. This was true in many cases of empyema during the influenza epidemic of 1918-19; it is to be explained by the coëxistence in the same lung of empyema and bronchopneumonia. Surely it was not due to the character of the pus itself, i.e., because it was thinner than that in pneumococcus empyemas.

LABORATORY FINDINGS.—*Blood.*—An inflammatory leukocytosis is the rule in cases of primary pneumococcus empyema and in those following acute lobar pneumonia. In such cases the leukocytosis is due to an increase of the polymorphonuclear finely granular cells, and the white-cell-count curve will run roughly parallel to that of the temperature. In cases of pneumococcus empyema following pneumonia, it is the continuous elevation of the leukocyte count, together with the slight fever, which leads to the correct diagnosis. This leukocytosis is valuable in excluding serous effusions. In the empyema prevalent during the influenza epidemic, however, a very different state of affairs existed. Some were similar to those with acute lobar pneumonia, but in many others there was no leukocytosis, but on the contrary there was a very low count (under 3,000 per cm.) during the bronchopneumonia and the empyema.

Blood Cultures.—Brooks and Cecil[9] made blood cultures in 20 of 80 cases of influenza-empyema. In 3 the cultures were positive, 2 for pneumococcus, and 1 for *Streptococcus hemolyticus*. Of these 3 cases 2 recovered. In the other 17 cases the blood was sterile. The fact that in empyema following acute lobar pneumonia the blood culture is practically always negative would indicate that this empyema is not a part of a general septicemia, but is due to direct extension of the lung infection. This view is borne out also by the infrequency in lobar pneumonia of definitely metastatic infections.

The exudate in empyema varies greatly in color and consistency. No very sharp line can be drawn between a serous and a purulent effusion. All gradations may exist, and yet one is seldom in doubt. The clear serous effusion of serofibrinous pleurisy is very distinctive, as is the thick purulent fluid of pneumococcus empyema. The doubtful fluids are practically all streptococcus empyema. In the pneumococcus cases, the fluid is rather thick, so thick even that it will not flow through a large needle; it is greenish yellow in color and often has a rather stale odor. In the *Streptococcus hemolyticus* cases the fluid has a light yellow color with a greenish tinge; in the early stages it is only slightly cloudy, but later it becomes definitely purulent. The turbidity is due chiefly to pus cells. In streptococcus cases the chains of organisms in the fluid often consist of from two to ten large cocci. In this group it is easier to find the pathogenic organisms than it is in the pneumococcus cases. Various flagellates, including *Lamblia intestinalis,* have also been found in the fluid.

The blood-pressure in empyema shows no characteristic changes.

ROENTGENOLOGICAL EXAMINATION.—The roentgenological examination of the chest is of great value in the diagnosis of empyema, especially of the encysted cases coëxisting with pneumonia. Stereoscopic plates should be made with the patient in the upright position, if possible. Special devices have been introduced to raise the patient to an upright posture without exertion on his part. This method of examination is not infallible, since the plates sometimes show no fluid where later it may be found, and *vice versa,* yet it is a very valuable method of examination. Sometimes it is the only way to locate an encapsulated empyema. There is very great danger of error if the fluid happens to be encapsulated in the left inner and posterior angle of the thorax, in which case its shadow is observed by that of the heart. The use of this method will save the patient many futile punctures, and whenever possible it should be used to guide the needle when the puncture is made. In empyema the shadow often shows the pus in a thin layer between the chest-wall and an only partially collapsed lung and reaching practically from diaphragm to apex, a condition seldom if ever seen in cases of serofibrinous pleurisy.

EXPLORATORY PUNCTURE.—The actual demonstration of fluid by exploratory puncture is the only clear proof of fluid in the chest. The spot for the insertion of the needle should be carefully located with the *x*-ray, if possible. If this is not possible, it is certainly much better to insert the needle repeatedly than to overlook an encapsulated exudate. A fine needle should never be used, since the thicker exudates cannot be sucked through it.

Diagnosis.—In children the pleura seems to develop a remarkable tolerance to the presence of pus, and the empyema may consequently be quite unsuspected for a long time. Therefore, in a child, a gradually developing pallor with weakness, sweats and irregular fever should suggest empyema, even in the absence of symptoms suggesting thoracic disease. The displaced heart will be of great diagnostic value in these cases.

In differential diagnosis, the same points are to be considered as in serofibrinous pleurisy, but the danger of confusion with acute lobar pneumonia is greater, especially when the pneumonia is early, before the consolidation is complete, when there is dulness but not yet flatness on percussion, and mere suppression of the breath and voice sounds. There is also danger of confusion, in a case of pneumonia, later, during resolution, after the bronchial breathing has become less distinct.

Complications.—A pneumothorax sometimes complicates an empyema. This may be the result of tapping, or it may occur spontaneously. It was found in 6 of the 36 cases of *Streptococcus hemolyticus* empyema reported by Brook and Cecil, and its presence was suggested in still other cases. It may occur very early. In these cases it was probably due to the rupture of minute subpleural pulmonary abscesses. It is rare in pneumococcus empyema.

An interesting feature of the pneumonia following the epidemic of influenza in 1918 consisted in the areas of *interstitial pneumonia* which developed between the lobules of the lung. Acute lobar pneumonia is a surface disease, for the alveolar epithelium is a surface membrane, and the exudate in croupous pneumonia is practically confined to the lumen of the alveolar spores, that is, on the surface of the body. In many cases of influenza-pneumonia, however, the inflammatory process involved also the interstitial tissue between the alveoli. This extra-alveolar exudate cannot resolve as does that within the air-spaces. Each area of interstitial pneumonia is in fact a potential abscess. These miliary abscesses sometimes lead to lung abscesses, while those just under the pleura can easily explain an empyema or a pneumothorax or both.

Pleuropericarditis is a not uncommon complication. It occurred early in the *Streptococcus hemolyticus* empyemas. Pericarditis was present in 9 of the 27 cases reported by Brooks and Cecil; 8 were streptococcus infections and arose by direct extension of the inflammation in the left lung, probably along the lymphatics. There is sometimes considerable exudate in the pericardial sac, sometimes as much as 900 c.c. Its presence may be indicated by the physical signs of pericarditis with effusion, including a pericardial friction-rub, and by the *x*-ray plates. The fluid is, in general, similar in character and bacteriology to the pleural fluid, although it is apt to be more hemorrhagic.

Endocarditis is not rare in pneumococcus cases, and is usually of the acute, ulcerative type.

The tuberculous empyemas are usually accompanied by *pulmonary tuberculosis* and often by tuberculous pericarditis or tuberculous peritonitis.

Certain cases show *mixed infections, e.g.*, a pneumococcus infection of the lungs and a streptococcus infection of the pleura. The involvement of the lung may be lobar or lobular, or lobar in one lung and lobular in the other.

Abscess of the lung was reported in 5 of the above-mentioned cases. The abscesses are usually small and multiple.

Pulmonary infarcts were present in 2 cases, one due to the pneumococcus and the other to *Streptococcus hemolyticus.*

Acute general *peritonitis* occurred in one, a streptococcus case. Purulent *otitis media* is a rare complication, seen especially in children. It usually develops on the same side as the empyema. This is given as evidence that it is not a metastatic infection, but one from the nose and throat, since the ear on which the child lies is the one infected, and this would be the side of the empyema. Acute suppurative meningitis developed in one case; this was also due to a streptococcus. It is well to observe that these cases with complications are infrequent and that the disease is essentially not a septicemia.

An encapsulated empyema may *rupture* externally through a bronchus (and in such cases the prognosis is usually good) or into the pleural cavity. Thomas[10] reported 2 cases showing the latter course. One occurred in a boy of thirteen who died in thirteen hours with a diagnosis of some acute abdominal condition; the other patient was in a desperate condition, but was saved by operation. Thomas insisted that in all such cases the diagnosis should be made early and that interference should be prompt. These patients complained of a sudden sharp pain in the chest on exertion, and in a few hours they were very ill with signs of abdominal trouble: pain, abdominal distention, a temperature of 104° F. (40° C.), respirations from 50 to 60, pulse 140, and leukocytes 71,500 in one case and 41,000 in the other. The same author calls attention to the danger from the exposure of the pleural surface to the pus, and to the sudden reaction of the pleura by the formation of an acute exudate. He also mentioned the absence of vomiting which is so common in acute peritonitis.

Sequelæ.—In unoperated cases and in those in which the operation is made late in the disease, and in which, therefore, the pleura is considerably thickened, the retraction of the chest is apt to be more marked than it is in a case of serofibrinous pleurisy. In some cases pleural cysts form between the layers of the thickened pleura. In unoperated cases and in those which relieve themselves by spontaneous rupture externally or through the bronchial tree, there may be a maximum grade of secondary thickening of the pleura with great retraction of the chest and permanent carnification of the lung. In this condition the lung is airless and, therefore, functionless. These changes in the parenchyma of the lung may lead to bronchiectasis. The inspissated pus in such cases may in after years become calcified, while in other cases the fluid even forty years later may be thick, lemon-yellow in color, cheesy-looking and very rich in cholesterin (9.73 per cent. of the fluid, and 56.1 per cent. of the total solids).[11]

Association with Other Diseases.—ACUTE LOBAR PNEUMONIA.—Empyema is one of the most important sequelæ of acute lobar pneumonia and of epidemic bronchopneumonia. Vaughan and Schnabel[12] reported empyema in 13.5 per cent. of the cases of lobar pneumonia which came under their observation during the influenza epidemic of 1918-19. Brooks and Cecil reported empyema in 80 of their 306 cases of pneumonia. Of these 80 cases 15 were due to pneumococci and 50 to streptococci, the most of them to *Streptococcus hemolyticus.* In 15 the pus was sterile. The pneumonia was either bronchial or lobar in type. The bronchopneumonias were associated with streptococcus empyemas, the lobar with pneumococcus empyemas. Usually the organisms of the lung and of the pus were identical, but in 9 cases of pneumococcus pneumonia the empyema was due to a streptococcus. The onset of the pneumonia and of the empyema is often simultaneous, especially in the streptococcus cases. In the epidemic of 1918, a large number of cases of empyema were due to the pneumonia following measles. These were all streptococcus cases, and the mortality of this group was the highest of all, 61.5 per cent. In the series reported by Brooks and Cecil the pneumonia followed influenza, tonsillitis and many other mild infections. Two cases of streptococcus empyema followed the pneumonia of mumps. In the group of 115 cases of empyema reported by Beals, Zimmerman and Marlow[13] the majority were due to a hemolytic streptococcus, while over 80 per cent. of these cases gave a definite history of antecedent acute bronchitis, pharyngitis, or tonsillitis.

Other diseases associated with empyema are pharyngitis, typhoid fever, infarction of the lung, hemorrhagic pleural effusion, infection of the pleura with the gas bacillus (*Bacillus perfringens*) and *Bacillus pyocyaneus.* Scarlet fever is often followed by an insidiously developing empyema. In typhoid fever, empyema, due to *Bacillus typhosus,* was found in 2 per cent. of the fatal cases, while it develops in many others during their convalescence.

Clinical Varieties.—BILATERAL CASES.—In some cases the empyema is bilateral. In these the mortality is very grave. The 7 cases reported by Vaughan and Schnabel all resulted in death.

PNEUMOCOCCUS EMPYEMA.—In nearly all text-books pneumococcus empyema is the variety described. It has therefore become the prototype of all empyemas. This form usually develops during the convalescence of the pneumonia. The temperature of the pneumonia falls at the usual time either by lysis or crisis, but instead of reaching normal, or after a brief period of apyrexia, it slowly rises again. At first one usually attributes this fever to delayed resolution. The cough persists, the sputum, now of a mucopurulent character, continues, and chills and sweats are common. The pulse rises with the temperature. The patient does not appear to be very ill. The physical signs of this form of empyema are frank, so frank that physicians have been misled as to the ease of recognizing pus within the chest cavity when it is due to other than pneumococcus infection. The most constant signs are flatness on percussion, and absence or very faint transmission of breath sounds. Voice sounds are more often transmitted than breath sounds. The pus is creamy and sometimes so thick that none is obtained through a fine hypodermic needle. It is very rich in pus-cells and usually contains many encapsulated diplococci. The pneumococcus found is usually Type I, II, IV. In 15 cases reported by Brooks and Cecil, 5 died, representing a mortality of 33 per cent. One case was complicated by endocarditis and septicemia. In another case, one complicated by perithyroid abscess, the blood culture was positive. In these fatal cases the deaths were early and apparently due to the pneumonia.

BRONCHOPNEUMONIA.—Bronchopneumonia is generally a definitely pyogenic infection of the lung, due to an organism which invades the interstitial pulmonary tissue and then, by direct extension, the pleura. The empyema which develops during an attack of bronchopneumonia is an early, rather than a late, complication, and is therefore often coëxistent with the pneumonia, a matter of great moment in therapy, since the evacuation of the fluid is a much more serious matter. The presence of the masses of consolidated lung in such cases modifies markedly the physical signs. This bronchopneumonia may be due to several organisms.

STREPTOCOCCUS HEMOLYTICUS EMPYEMA.—This is the form of empyema which predominated in the army during the epidemic of 1918-19. It is a rare type in civil life. This complication developed in 34.8 per cent. of the cases of the streptococcus pneumonia epidemic of the spring of 1918 at Camp Dodge, Iowa.[14] The incidence of empyema among the colored soldiers with pneumonia was 20 per cent., and their mortality was 44 per cent., while among the whites the incidence of empyema was 45 per cent.; 64.8 per cent. of these patients died. The general mortality of the 142 cases of streptococcus empyema was 60.4 per cent. Of the 80 cases which Brooks and Cecil reported, 36 were of this type; of these 22 died, representing a mortality of 61 per cent. This clinical picture is fairly characteristic. As prodromal symptoms the patient often complains of recent infection of the upper respiratory tract. The onset is gradual rather than sudden. Pain in the side may add to the respiratory distress, but it is very inconstant and not severe. The cough is generally dry, and often it is altogether absent. The fever is irregular, suggesting a septic infection. The diagnosis at this stage is usually influenza or bronchitis. The sputum, when present, is rather characteristic: yellowish, mucopurulent and viscid, very rarely rusty or hemorrhagic, even though during this period definite pneumonia is present. The pulse is usually slow at first, and in general runs parallel to the temperature. The respiratory rate is high throughout the course of the disease.

Before the empyema has developed the physical signs are very indefinite. Sometimes there is an area of dulness on percussion, over which moist crackling râles are the rule. Voice and breath sounds are faint.

The presence of the empyema is usually definite in from four to five days after admission. In other cases it develops with surprising rapidity and, unless roentgenology is employed, is often present before one can be sure even of the presence of a pneumonia.

This empyema develops during the pneumonia and, therefore, is not a sequela. It is often a surprise at the autopsy table, so disappointing are the physical signs. For this reason exploratory punctures and roentgenograms should be made in all doubtful cases.

The development of the empyema is sometimes attended by no alteration in the clinical picture, and by strikingly few alterations in the physical signs. Profuse sweats are one of the most constant signs. These are similar to those in acute rheumatic fever. The chills are never present after the onset, even with the sweats. The general exhaustion is more pronounced than in pneumonia, and should suggest an empyema whenever it is out of proportion to the physical signs. An acceleration of the respiratory rate is of suggestive value. Temperature and pulse show nothing distinctive unless the empyema develops after lysis has begun. The alteration of the percussion note is very valuable. Abdominal rigidity is usually absent. The zones of hyperesthesia of Head are not present. Stabbing pains are either absent or slight. The skin is tender on gentle percussion, but is not hyperesthetic. This tenderness, deep and not superficial, is often a great help in deciding upon the place at which to insert the needle.

Outspoken pneumothorax was present in 6 of the 36 cases mentioned and was possibly present in others. This was due to the rupture of the subpleural miliary abscesses, and is an early complication. Pleuropericarditis is also an early and rather common complication.

The leukocyte count is of very little value in determining the development of *Streptococcus hemolyticus* empyema in a case of bronchopneumonia.

The fluid on aspiration is of a light yellow color with a greenish tinge and, at first, only slightly cloudy and slightly purulent. The cocci are numerous, large, round or slightly flattened, and in chains of from 2 to 10. After twenty-four hours of incubation on blood-agar plates, the cultures from the fluid show small, elevated, opaque colonies of a pearl-gray color, each surrounded by a sharply defined zone of hemolysis. Sub-cultures in blood-broth give a diffuse and cloudy growth with a heavy sediment. The blood-cells are rapidly destroyed; therefore the broth becomes of a claret-red color. The smears of these cultures will show chains of streptococci.

Of the 22 patients who died, 17 came to autopsy. Of these the pneumonia in 11 was bronchial in type and in 8, lobar. In one-half of the cases the pleural fluid was free, in the other half, sacculated. The fluid was sometimes cloudy and sometimes purulent. The common location for a saccule was between the pericardium and the anterior flap of the left lung, which explains the frequent occurrence of pericarditis in such cases. The lungs also showed an interstitial pneumonia.

STREPTOCOCCUS VIRIDANS EMPYEMA.—Of the above-mentioned 80 cases, 4 were of this type; 3 of these died, representing a mortality of 75 per cent. These non-hemolyzing streptococci were found both in the sputum and in the pleural exudate of these patients. The course of this disease differed in no way from the one due to *Streptococcus hemolyticus*. In all cases the pneumonia was of the bronchial type, that is, the consolidation was in patches and the empyema was sacculated. The fluid was cloudy, yellowish in color, and full of fibrin flecks. Ballin,[15] reporting the cases of empyema at Camp Grant, September-October, 1918, sharply differentiated the empyema following hemolytic streptococcus pneumonia from that following influenza-pneumonia. In the former group the empyema develops early in the pneumonia, on the fourth or fifth day, the exudate accumulates in such large amounts that it is even dangerous because of its mere quantity, and, therefore, it should be aspirated early. The fluid is thin, grayish-red in color, turbid, because of the presence of fine fibrin flakes, and it becomes truly purulent much later. In the influenzal empyemas which Ballin observed, the pneumococcus seemed to be the predominating organism, and yet the pneumonia is very different from the ordinary lobar pneumonia, being a very virulent necrotizing bronchopneumonia. He says that this organism presents some difference from the usual pneumococcus "as to typing, etc." He does not know whether it is a very virulent strain or whether it is associated in this infection with some other organism. The influenza empyema developed late in the course of the pneumonia (in from the first—rarely—to the fourth week). These cases are frequently complicated by multiple metastatic abscesses in various parts of the body. The exudate is small in amount and, when abundant enough to aspirate, it is too thick to flow through an ordinary trocar.

Streptococcus empyemas sometimes complicate pneumococcus pneumonias. In the 80 cases of Brooks and Cecil, 9 showed this mixed infection, while in 1 case the empyema was due to *Staphylococcus aureus*. *Streptococcus hemolyticus* and *Streptococcus viridans* were found in the fluid, while the lobar pneumonia was due to the second, third and fourth types of the pneumococcus. Of these 10 cases, 6 died, representing a mortality of 60 per cent.

Sterile Empyemas.—Of the above-mentioned 80 cases, the fluid in 15 was sterile. In a majority of these it was purulent or semi-purulent in character. Although the cultures were sterile, yet, in smears of the fluid from all of these cases, disintegrated Gram-positive cocci could be seen. Ten of these 15 cases accompanied a lobar pneumococcus pneumonia. Of these 10 cases, 5 died, representing a mortality of 50 per cent. The other 5 accompanied a streptococcus pneumonia. Of these, 2 died.

Diaphragmatic Empyema.—Diaphragmatic pleurisy is usually fibrinous in character, involving a part or the whole of the diaphragmatic surface. Pleurisy with effusion might begin as a diaphragmatic pleurisy, but the fluid would soon obliterate all characteristic signs of the diaphragmatic involvement. Cases with circumscribed, that is, encapsulated, serofibrinous exudate between the diaphragm and lung, occur, but are rather rare, while in other rare cases an empyema may be limited to this region of the thorax. The signs of an encysted exudate in the diaphragm, whether serous or purulent, may be very indefinite if the effusion is small. It may, indeed, be impossible to recognize it by physical examination, and the first symptom may be the rupture of pus through the lung. The *x*-ray plates, however, will probably help, although, if the pus is in the posterior complemental spaces or in the posterior mediastinum, in the shadow of the heart or liver, this may not be of assistance.

ENCYSTED PLEURISY.—In from 3.2 per cent. to 3.4 per cent. of all cases of empyema the fluid is encysted. In these the fluid, usually small in amount, is enclosed in a definite cavity formed by a recent fibrinous membrane in the pleura or by old adhesions. As a rule there will be but one such collection, but in a few cases the exudate has been found in several loculi which may communicate. The fluid is nearly always purulent, rarely serous. The location of these encysted empyemas is usually the lower posterior chest between the lower lobe at its edge and the parietal pleura, or in the fissures between the lobes, or between the diaphragm and the lung, or between the lung and the pericardium, or between the parietal and visceral pleuræ below and posterior. In some of these cases the encysted empyema represents a small fraction of originally free fluid, most of which has disappeared, while some has become limited by adhesions. As a matter of fact, with the exception of massive empyema, all cases of empyema sooner or later become encapsulated as they dry out, unless they are opened by operation.

In another group of cases, especially those in which the lesion is situated in the fissures between the lobes, the starting point of an empyema is a small pulmonary abscess which ruptures into the fissure and starts there a local empyema. The possibility, however, that an empyema encapsulated in a fissure may have perforated into the lung and caused a lung abscess must not be overlooked.

The amount of pus in the portions of the pleura walled off by adhesions will vary from 1 to 2 ounces to about 2 pints.

The general symptoms of encapsulated empyema are those of an ordinary empyema, but many cases are very latent and are not suspected, since the parietal pleura is not involved until the pus perforates through into the general pleura or through the lung. Cough with sputum, pain on respiration, and striking physical signs, may be entirely absent. If, on the other hand, the parietal pleura is involved, one would expect considerable pain and cough. The physical signs in a typical case are a local area of dulness on percussion; vocal fremitus absent in cases with much pus, but more often increased by the adhesions which wall in the fluid; and, usually, faint bronchial breath sounds with few or no adventitious sounds.

INTERLOBULAR PLEURISY.—In every case of general pleurisy there will also be an interlobular pleurisy, which will glue the layers of pleura in the fissures between the lobes. This often leads to the formation of pockets in which fluid may accumulate. In other cases the pleurisy is limited to the fissures between the lobes. These interlobular pleurisies are usually tuberculous in character, although during the last epidemic the number due to the rupture of small pulmonary abscesses into the interlobular spaces was evidently rather large. These cases have the symptoms and physical signs of lung abscess, which indeed they are, since they are a collection of pus entirely surrounded by the lung. Like pulmonary abscesses they may perforate through the bronchi.

In chest diagnosis it is well to bear in mind the surface anatomy of the lung, since in any case with physical signs of abscess or tumor along the line of a lung fissure interlobular pleurisy should be thought of. These abscesses act as foreign bodies, and, as a result, cause cough and expectoration.

About 93.6 per cent. of the cases of pulsating pleurisy are located on the left side. Some of the effusions are serous, but most are purulent. Most of these cases are tuberculous in character and the next largest number is post-pneumonic. These patients are more often men than women. No good explanation has been given for the transmission of the cardiac beat in these cases.

Treatment.—The **pus** in a case of empyema should be **removed** just as soon as it is discovered, no matter how sick the patient is. No temporizing methods are justified. The manner or removal will depend in large measure upon the nature of the case, upon the organism found in the pus, and upon the stage of the disease. In the ordinary pneumococcus empyema which follows the resolution of an acute lobar pneumonia one promptly **resects a rib and drains.** In children with pneumococcus empyema simple **aspiration** is often sufficient, even though the fluid is definitely purulent; but in adults such treatment is hardly safe. In the cases of streptococcus empyema, which prevailed before the epidemic of 1918-19, the excision of one rib was a common operation; sometimes two were excised to permit the freest possible drainage. One of the most important and surprising lessons of the last epidemic was the seriousness of such an operation in those empyemas which accompany, not follow, a (usually) streptococcus bronchopneumonia. The mortality in those cases drained by early operation (while the fluid was still fairly clear and organisms were present) was 52 per cent. or over, while in another series of similar cases in which the fluid was aspirated at once and operation was deferred until the pneumonia ran its course and the fluid was purulent, the mortality was only 10 per cent. In this epidemic the method adopted was the early and repeated removal of the pus by aspiration through a needle, until the pneumonia subsided. Meanwhile the pneumonia was treated and the general health of the patient sustained by the early use of **digitalis, camphor, caffein,** *etc.* The cough is of no advantage to these patients and should be controlled by **codein, morphin,** etc. Later the chest is opened at one or two points and drained thoroughly. In some critical cases immediate operation seems unavoidable.

Swabbing out the cavity of the pleura with sponges on long forceps is recommended by some. Others would flush out the pleural cavity every three hours with some weak antiseptic fluid by means of Carrel tubes. Still others use the Carrel-Dakin fluid in drainage. After operation the chest cavity is drained freely until it is obliterated; then the operation-wound is allowed to heal. Berard and Dunet urge that as soon after operation as the temperature becomes normal, which will occur as a rule on the third or fourth day, the patient should be required to walk around the room regularly, since this ambulatory method has seemed to favor better drainage and better expansion of the lung. The patients thus treated are said to be well in from fifteen to thirty days without loss of weight or subsequent deformity of the chest.

Garbat[16] considers the bacteriologic control of the cavity important in the proper treatment of empyema, if, as is recommended, the **Carrel-Dakin method of disinfecting the pleural cavity** is employed. It is stated that cultures should be made periodically from exudate obtained directly from the cavity and also from the sinuses leading into the empyema cavity, and that the wound should not be allowed to close until these are sterile on repeated cultures. A persistently high bacterial count or a sudden increase in this count is reasonable basis for assuming that there is some complication in the healing of the empyema cavity.

The fluid may be obtained with a platinum loop passed into the empyema cavity. The secretion should be thoroughly washed off from the loop into the Petrie dish with a 1/10 to 2/10 c.c. of sodium thiosulphate solution to stop the further action of any Dakin solution present in the secretion. The melted blood-agar medium is then added and the plates poured at once. Each plate should consist of 10 c.c. of melted agar poured into a test-tube containing 1 c.c. of sterile defibrinated human blood; the mixture should then be emptied into the Petrie dishes containing the exudate, mixed well and inoculated for twenty-four hours. The number of colonies is then estimated.

The empyema cavity should not be flushed with the Dakin solution for at least six hours prior to the making of the culture. A gradual decrease of the organism may be expected under the treatment, until the cavity is sterile. If this does not occur, it may mean that there is some pocket which opens into the cavity which the tubes do not drain, or that the necrotic tip of a rib projects into the cavity, or that a piece of gauze was left in the wound at operation, or that there is some error in making up the fluid. After the empyema cavity has become sterile the sinuses should be well tested. As a rule there will be more organisms and a greater variety of them here, since the sinus is not drained by the Dakin fluid as much as is the cavity. If the sinus is allowed to close too early, these organisms will reïnfect the cavity.

During the convalescence it is desirable to prescribe **pulmonary gymnastics** to inflate the lung. This is easy, if the operation was early, but difficult, if the lung is adherent and bound down in an unnatural position. The Wolf bottles, two large bottles so connected by tubes that the patient can blow the water from one bottle over into the other, are often used. One criticism of this method is that it tends to over-distend the normal lung rather than inflate the collapsed one. If possible, the normal side of the chest should be fixed during any exercise. The patient may sit in a chair which has a side round so located that it can be grasped with the hand of the good side as the arm hangs vertically. With each deep breath the patient pulls forcibly on this arm, thus fixating the good side of the chest. When the patient is walking he can flex the arm on the good side behind him, grasping the elbow of the other arm, which hangs vertically and rigidly. Then, with each deep breath, the patient contracts the flexed arm as strongly as possible, thus fixing to a certain degree the good side. In those cases in which the collapsed lung is so firmly bound down in a pathological position that its ultimate expansion seems impossible, operation to obliterate the cavity is often desirable, although not always satisfactory.

During the convalescence, after an attack of empyema, the patient should be in the open air and sunshine. The cough, which in these cases is often of distinct disadvantage to the patient, may be controlled by morphin or codein. Hydrotherapy and full diet may be recommended.

Prognosis.—There are several possible terminations of the empyema. First, death may result, usually due to general septic intoxication, but also due to general systemic infection. Second, the chest may become contracted. The complete absorption of pus is impossible, but smaller effusions dry out from the absorption of the serum and the pleura becomes greatly thickened, encapsulating the inspissated pus, in which lime salts may later be deposited. The deformity of the chest-wall in such a case is often serious. Third, the pus may perforate the lung. If it finds its way into the bronchial tree through a small fistula which permits only slow evacuation, the prognosis is, in general, good. The fistula between the pleural cavity and the trachea may in such a case remain open for some time. In some cases of empyema, especially those due to streptococcus pneumonia, a pneumothorax may develop through a fistula which connects the pleura and the bronchial tree, but this is unusual. In still other cases a definite fistula into a bronchus may not form, but the pleura may become necrotic and allow the pus to seep through the lung-tissue to the bronchi. Again the pus may perforate through the chest-wall (empyema necessitatis) and the patient may thus recover by natural surgery. In the majority of such cases the perforation is in the fifth (from third to sixth) interspace of the lower anterior or lateral portions of the chest. The pus may escape from several fistulæ or through one long fistula, which may follow a circuitous route in the chest-wall. If the tumor formed by the empyema before its rupture is near the heart, it may pulsate. These fistulæ may remain open for years. The pus may perforate into the esophagus and be evacuated through a pleuro-esophageal fistula. In one such case reported by Osler, this fistula also had an external opening which, therefore, connected the pleural cavity with the exterior, through the chest-wall, and also with the esophagus. The pus may perforate into the peritoneum, the pericardium or the stomach. In other cases the pus may burrow its way to the iliac fossa, causing a lumbar or psoas abscess.

The prognosis in empyema will depend in large measure upon the causative organism. In the pneumococcus variety it is favorable, since these cases are usually local infections from the lung. Streptococcus empyema, however, is usually part of a general septicemia, or results in this, and the prognosis is worse, not only because of the character and virulence of the organism, but because of the many and widespread infections which may develop. The mortality of the streptococcus group following measles in the 1918 epidemic was very high (61.5 per cent.). If the pus is sterile, the case is usually one of tuberculosis. The mortality figures in the various varieties of empyema are given in the section describing those forms of the disease.

Pathology.—In pneumococcus empyema the pus is usually thick and creamy in character, with a rather stale, sweetish odor. If allowed to stand, it separates into two layers, a fairly clear, greenish-yellow layer of serum, and a thick layer of pus-cells. In streptococcus cases the fluids may be of any grade of turbidity, some being almost clear, others as thick as that of a pneumococcus empyema.

The layers of the pleura are greatly thickened and are covered with a fibrinous exudate, from which streamers may float into the fluid and form a shaggy membrane. In pneumococcus cases the thick layers of fibrin may be easily stripped off. If the case is one of long standing, widespread organized adhesions will form between the pleural surfaces, and thereby fix the lung in a pathological position. In many cases without early operation the visceral pleura immediately adjacent to the pus becomes adherent to the chest-wall, thus forming an abscess cavity and also anchoring the lung in an abnormal position. Later the parietal pleura increases in thickness. The pus may have ruptured through the lung, the chest-wall or the diaphragm. The pleural surface may show ulcerations, or saccular abscesses may develop in the thickened pleura. If the abscesses are small and have not been evacuated, the inspissated pus may become calcified. In a few cases the empyema is bilateral. The collapsed lung, if allowed to remain for some time unexpanded, may become fibroid and useless for respiration. This explains most cases of unilateral fibrosis of the lung.

The surface of the diaphragm may also become thick and stiff, because of the fibrinous exudate which later becomes organized. Later its muscle tissue may atrophy and the diaphragm become a hard, fibrous membrane with almost no muscular power. This crippling of the diaphragm as an organ of respiration, both during the acute period when it is swollen and stiffened by the fibrinous exudate and later after it has been transformed into a fibrous partition, has an important effect upon the health of the patient. The diaphragm may, indeed, no longer form a convex dome projecting up into the thorax, but it may become permanently concave.

HEMORRHAGIC PLEURISY

In hemorrhagic pleurisy the pleural exudate contains so much blood that it gives its color to the fluid. Such fluids are met with in cases of malignant disease which involve the pleural surfaces; in tuberculosis, in which cases the hemorrhage is attributed to the erosion of a blood-vessel by the tuberculous process; in various asthenic conditions, including Bright's disease; in cachexia due to cancer of other parts of the body; in cirrhosis of the liver, and in rare cases of the malignant type of acute infectious fevers. The most important cases are those of malignancy, and this should always be suspected if the pleural effusion is hemorrhagic, not only in persons over forty years of age, but especially in children with hemorrhagic pleurisy.

Trauma of a blood-vessel due to accident, especially to an accident from the needle used in aspiration of the chest in cases with serous or purulent effusion, is an important cause. In order to avoid the intercostal arteries, the needle should be introduced over the upper edge of a rib rather than at the upper margin of an interspace.

Richet and Barbier reported 5 cases of influenza in which a blood pleurisy appeared from the fifth to eighth day of the influenza. The pleural effusion was almost pure blood. This character of the fluid seemed to have very little effect upon the course of the disease. In conclusion, bloody pleural effusions have been found in apparently healthy persons, due to causes as yet undetermined.

NON-INFLAMMATORY EXUDATES WITHIN THE PLEURA

PNEUMOTHORAX

Pneumothorax, or the presence of practically only air in the pleural cavity (a little blood or an amount of serum too small for detection on physical examination may for the present be disregarded), has been classified as: (*a*) simple primary pneumothorax, (*b*) spontaneous pneumothorax, (*c*) idiopathic pneumothorax and (*d*) essential pneumothorax. If an appreciable amount of serous exudate is also present, the condition is one of hydropneumothorax; if of pus, it is one of pyopneumothorax.

Etiology.—A simple pneumothorax may develop at any age from causes which cannot be determined. It even occurred in one infant two days old. The child recovered.[17]

Among the external wounds causing pneumothorax may be mentioned:

1. Broad gashes
2. Bullet wounds
3. Punctured wounds
4. Fractured ribs

The mechanism protecting the pleural cavity is well illustrated by these cases of fractured ribs, since pneumothorax will develop only in a small per cent. of them, even though the visceral pleura is torn, and that this is torn is proven by the subcutaneous emphysema which often develops over the wound.

Severe crushing of the thorax without fracture of the ribs, as in accidents in which the patient is run over by heavy vehicles, may, especially in the young, cause pneumothorax. But as a rule, in such cases, the lung ruptures while the pleural membrane does not, but at first protects the pleural cavity while the air escapes into the subcutaneous tissue at the suprasternal notch. Later, however, these cases may develop a spontaneous pneumothorax. It is in these cases that diaphragmatic hernia must be excluded. The cases due to the accidents of aspiration are rather common. The visceral pleura may be torn by a trocar or even by a hypodermic needle, which allows the air to enter the pleura from the bronchial tree, or the air may enter directly through an open aspiration needle. It is for this reason that this needle should be connected with a vacuum bottle or with a tube full of water before insertion or before the withdrawal of the stilette, since in the case of many small effusions a negative pressure still obtains in the chest.

The spontaneous primary cases seem to be due to lesions resulting from a strain suffered perhaps years before. This occurs especially in young men under forty years of age. Tuberculosis is, however, the great cause of pneumothorax, explaining over 90 per cent. of all cases.

SIMPLE PRIMARY PNEUMOTHORAX.—Simple pneumothorax,[18] or the presence of air, but no fluid, in the pleural cavity, might arise in several ways: a clean wound of the visceral pleura, such as that produced by a penetrating instrument; or, the rupture of an emphysematous bleb of pleura—the most common cause—or, a tear of the pleura—following exertion—at the edge of a mass of adhesions. In all other groups of cases of pneumothorax, and especially those due to pulmonary disease, as tuberculosis, the pleural cavity may contain air only, and yet a hydropneumothorax or pyopneumothorax is the rule. In the rare cases of pneumothorax without an effusion, and due to active disease, the condition would be termed simple secondary pneumothorax, while the term simple primary pneumothorax would be reserved for cases not due to an active necrosis-producing disease of the lung and pleura.

The mere presence of air in the pleura does not cause inflammation, and so an exudate need not of necessity develop. The air, by interchange with the gases in the capillaries of the pleura, will quickly become a gas mixture practically equal to that of capillary blood. (The use of nitrogen gas in the artificial pneumothorax treatment of pulmonary tuberculosis is a sad proof of the lack of clinical laboratory work in connection with the wards.) The balance in gas osmosis will always be toward the blood stream. (We have no evidence that it is ever in the opposite direction as was the firm belief for decades). If the pleural surface is in some measure normal and the fistula which admitted the air is closed, there will be steady, although slow, disappearance of the pneumothorax.

One might think at first that a pneumothorax would be complete; that is, that an opening which would allow any air at all to enter the pleural cavity would allow enough to rush in to satisfy completely the elastic recoil of the distended lung, that the lung would at once collapse and that the pressure in that cavity for a moment at least would be atmospheric pressure. But practically this seldom occurs. The air would enter in gusts during inspiration, through an external wound artificially held open, and be partly blown out again during the next expiration. But in case of a bronchopleural fistula it would enter the pleural cavity during inspiration or expiration—chiefly the latter—according to the size of the fistula, the rigidity of its walls, and the type of respiration.

The ideal wound to produce a complete pneumothorax might seem to be a broad gash in an intercostal space such as frequently resulted in the Middle Ages from duels. But such wounds even when they were large enough and were suitably situated, instead of producing pneumothorax, were often followed by hernia of the lung. So difficult was it to reduce this hernia that the surgeons of that period either made the wound larger, so that they might push the lung back, or burned off the protruding lung by actual cautery. It is natural that they and the physicians of later centuries would not accept the idea of an interthoracic negative pressure, for their experience would indicate the presence in the chest of a very powerful positive pressure. The explanation of these hernias is simple; indeed, a surgeon may observe hints of the mechanism which produces them during almost any operation for empyema. The negative pressure in a normal chest, important though it is, is small, varying from —5 mm. Hg at the end of quiet inspiration to —2.5 mm. Hg at the end of quiet expiration, while forced expiration can create a positive pressure of at least 100 mm. Hg and strong inspiration a negative intrapleural pressure of 30 mm. Hg. Following an open wound in the thorax the patient, with his glottis partly closed, especially during expiration, tends to make reflex inspiratory and expiratory efforts in rapid succession, and so creates and maintains a relatively high positive pressure within the bronchi which forcibly reïnflates the lung, and, if the wound is properly situated, would force it through the wound.

At this point the author would call attention to the very important fact that in practically all cases of pneumothorax, except those in which the lung on the affected side is so diseased by tuberculosis or so bound down by the results of a previous empyema that its distensibility is quite gone, the lung on the side of the pneumothorax will continue to carry on a fairly efficient respiration even in the presence of an open external wound, unless this wound is of such size and character that air enters through it much more easily than through the trachea; however, this is seldom the case.

A penetrating wound which pierces the visceral pleura can, on the other hand, readily cause pneumothorax. For this reason men specially trained were in attendance at the medieval duels, who, in case of such a wound, would quickly apply their mouths and suck it vigorously, evidently to diminish the developing pneumothorax. The results were so satisfactory that the priests refused extreme unction to these wounded persons on the ground that such brilliant cures must be due to the devil. To-day not a few of our cases of pure pneumothorax belong to this group and are due to tears in the visceral pleura caused by fractured ribs, by the sharp needle used in exploratory punctures, by bullet wounds, etc.

The lung-tissue as it expands and contracts during respiration lends a valve-like action to the bronchopleural fistula which, therefore, tends to pump the air toward the periphery. This is much accentuated by the forcible spasmodic reflex respiratory movements which such a trauma stimulates. This is especially true of coughing.

SPONTANEOUS PNEUMOTHORAX.—Spontaneous,[19] also called "natural," pneumothorax is a term used of two groups of cases: first, those in which there is evident lung disease but in which the pneumothorax develops suddenly and without apparent adequate immediate cause, such as a strain, coughing, etc., and second, those which develop in apparently healthy persons. The condition in either group may follow an injury or exertion often quite inadequate to explain the rupture of the visceral pleura, such as gymnastic exercises, lifting heavy weights, straining at stool, running, jumping, dancing, stooping over, laughing, crying, coughing, sneezing, yawning, while in some cases it has developed during sleep. It is not uncommon that the pneumothorax follows several days after a severe strain. Certainly every case of pneumothorax must have an adequate cause, and the classification of types of disease should not be based upon our accuracy as diagnosticians. The term "spontaneous" should indicate the unexpected character of the onset, the lack of adequate immediate cause, whatever the pathological basis of the condition.

Since every case of pneumothorax is due to the rupture of the lung, a short discussion of this lesion may be in place here. Rupture of the almost normal lung by sudden increase of intratracheal pressure is an accident which may easily occur and which is not uncommon, as in influenza with its explosive, straining, violent paroxysms of coughing, in whooping-cough and in parturition, especially in the pre-chloroform days. The pleura, however, is not often ruptured. It is rather raised in blisters by the air which escapes from the ruptured lung-tissue; the air, dissecting its way along the bronchi to the mediastinum, escapes into the subcutaneous tissue at the suprasternal notch. These blebs of unruptured pleura which are thus dissected free from the lung-tissue must be of importance years later in the production of pneumothorax. Any disease of previous years which has created a weak spot in the lung, as well as any acute disease leading to pulmonary necrosis, provides the condition which may immediately or at some later date result in pneumothorax from a seemingly inadequate cause.

The use of the term "spontaneous" pneumothorax for those cases only which develop in apparently healthy persons is subject to the objections mentioned above, although the older and usually very objectionable term, "idiopathic" indicates better what the term implies, *i.e.*, the apparently causeless perforation of a lung which previously was presumably free from disease. The most probable cause of these cases is the rupture of an emphysematous bleb, which may have developed years before as the result of a severe strain, or which may have formed at the edge of the contracting scar of a healed tuberculous lesion. These blebs or blisters of pleura may be almost a centimeter in diameter. The tissue of these blebs of pleura is poorly nourished, and a progressive atrophy of the membrane must continue, until the pleura is ruptured by even a slight increase of intrabronchial pressure.

IDIOPATHIC PNEUMOTHORAX.—The term idiopathic pneumothorax was formerly used of cases, said to be numerous, in which the gas was supposed to be "secreted" by the pleural surface, or diffused into the pleural cavity, from the blood. Laennec held strongly to that view. Use is now made of this term to describe cases in which the gas is the product of gas-producing organisms growing in a pleural exudate. Other writers still use the term idiopathic to describe the spontaneous cases in healthy persons, cases which develop suddenly as the result of an insignificant cause, and in which the previous history is silent as to any disease or accident which might have weakened the lung. They test these persons with tuberculin to eliminate the suspicion of latent tuberculosis and, if this test is negative, they suggest for these cases an inherent weakness of the lung, that is, a congenital histological defect of the pulmonary tissue. It is needless to say that the more such cases are studied, the more evident it is that latent tuberculosis or strain in the past is the cause.

SECONDARY PNEUMOTHORAX.—Secondary pneumothorax is the form of this condition which is clearly a complication of a necrosis-producing disease of the lung or chest-wall. The most common cause by far is pulmonary tuberculosis. In these cases a sub-pleural tubercle may soften so rapidly that a protective pleurisy cannot develop and a bronchopleural fistula consequently arises. Abscesses of the lung, especially the miliary, subpleural abscesses of the influenzal interstitial pneumonia of the epidemic of 1918-19, may cause this condition. In these cases the pleural cavity may contain only air, but, as a rule, a serous or a purulent exudate will also develop.

HYDROPNEUMOTHORAX.—In hydropneumothorax the pleural cavity contains both serum and air. This is usually of tuberculous origin. The rupture of a subpleural tubercle will not only allow air to enter the pleural cavity but caseous matter also, which will infect the cavity, and a secondary pleurisy with effusion consequently develops. The exudate which follows the rupture of a tubercle or abscess into the pleural cavity may be purulent in character (pyopneumothorax). In some cases an empyema is primary to the entrance of air, or the development of air in the pleural cavity. Hemopneumothorax may follow trauma or rupture of an emphysematous bleb.

Symptomatology.—Nearly all cases of pneumothorax are at first valvular in character. As mentioned above, normal lung-tissue tends to make a bronchopleural fistula valvular. That is, the fistula between the bronchial tree and the pleural cavity is closed most of the time, but will be opened by any marked rise of intrabronchial pressure, such as that due to coughing, and as a result more air enters the pleural cavity (valvular pneumothorax). In advanced cases of tuberculosis the bronchopleural fistula may penetrate solid fibrous and caseous tissue and so remain open during all phases of respiration (open pneumothorax). In the majority of cases, however, the fistula is soon permanently closed by a firm fibrinous exudate (closed pneumothorax).

The *onset* of pneumothorax may be very sudden and severe, or so gradual that it is at first scarcely perceptible to the patient. Other cases are so latent that they are accidental discoveries of the clinical examiner or of the pathologist. Its development, in the spontaneous cases, follows relatively insignificant causes and in the tuberculous cases it does not immediately follow coughing as often as one would suppose. Even in these latter cases it seems to develop spontaneously, at a time determined evidently by the nutritional changes of the pleura covering a superficial cavity.

It is a general rule that the more normal the chest, the more severe will be the symptoms of onset of a pneumothorax. In spontaneous cases in the apparently healthy, therefore, the onset is especially severe. In such cases there is a sensation as if the chest were being squeezed in a vise. Some describe a pain which resembles an attack of angina pectoris, while in others the pain and dyspnea are so severe that patients become quite unconscious. Local chest pain at the point of rupture is an occasional symptom of onset. Dyspnea is a very important symptom. It may develop suddenly, increase rapidly, and reach an extreme grade, that is, from 60 to 64 breaths to the minute. This distress and dyspnea are certainly not due to the exclusion of a large amount of respiratory surface, since they are absent in cases of closure of the primary bronchus; they are, rather, a reflex from the pleural surface, and are toxic in origin. (It is claimed by the enthusiastic supporters of the artificial pneumothorax treatment of pulmonary tuberculosis that the dyspnea of tuberculosis is even relieved by the pneumothorax, which lessens the absorption of toxin from the diseased area.) In cases developing during the course of chronic tuberculosis, the change in the character of the cough and the cessation of sputum may be practically the only early symptoms.

The *course* of a case of pneumothorax will depend entirely upon the disease of which it is a complication. In certain cases of pneumothorax the patient will certainly die unless he is relieved; but in other cases a remarkable tolerance of the pathological conditions develops in about a week, and the pleura may contain air for years. The prognosis will depend upon the underlying disease. That of the pneumothorax alone is favorable.

PHYSICAL FINDINGS.—*Observation.*—The physical signs on inspection in pneumothorax are somewhat similar to those in cases of pleurisy with effusion, except that they are apt to be rather more pronounced. At first the patient will sit up straight in bed, and his expression will be anxious, but later he rests, usually on the affected side, although some patients assume other postures. One patient even maintained the knee chest position for fifty-six days. Distention of the chest obliterates the interspaces and often, in about 60 per cent. of cases, reaches a degree not found in any other condition. Distention is most marked in pneumothorax acutissima. It may, however, not be present. In fact, the side of the pneumothorax may appear to be smaller than the other.

The dilatation of the chest is by no means proportional to the increased intrathoracic pressure, nor is it entirely due to it. It is in part a protective measure designed to permit the maintenance of a respiratory oscillation of the intrapulmonary pressure sufficient to ventilate the lungs. In cases of pure pneumothorax the pressure of the gas in the chest has never been found to be above 9 mm. Hg, and in no case of pneumothorax with fluid exudate has it exceeded 17 mm. Hg. In most of the cases the pressure at the end of expiration will be zero, and a definite negative pressure will be created during inspiration. When the chest is dangerously over-distended, it is not because it has been inflated by a great intrathoracic pressure, but because the thoracic cage has assumed a more and more inspiratory position in order to keep the pressure at the end of expiration as near zero as possible. This continues until the chest-wall can increase the capacity of the thorax no more, since each gain in size is sustained by an increased volume of gas. The dyspnea, also, which is often very severe, is by no means proportional to the amount of distention of the thorax, any more than it is to the elimination of respiratory surface.

Subcutaneous emphysema of extreme grade, even four fingers' breadth in depth, may complicate a pneumothorax. This is especially true in cases due to external wounds and to fracture of the ribs. Generally, when both pleural membranes are wounded and the air from the lung apparently has its choice of the two destinations, the pleural cavity or the subcutaneous tissue, the path of least resistance is the one leading to the subcutaneous tissue, so efficient is the mechanism which protects the pleural cavity. Edema of the hand and arm on the affected side has been reported as an early symptom in pneumothorax. Striæ atrophicæ rarely develop on the chest as a result of overdistention.

In no other condition does the liver descend to as low a point in the abdomen as it does in right-sided pneumothorax. In the average case the lower margin of the liver reaches from 2 to 10 cm. below the costal border, and yet the entire liver may be in the iliac fossa. This is especially true in cases of pure pneumothorax. The presence of a groove at the costal border suggests that the liver has been much depressed. In pneumothorax of the left chest the diaphragm is depressed even below the costal border.

Position of the Heart.—The dislocation of the heart is more extreme in pneumothorax than it is in any other condition. This is one of the first and most reliable physical signs of pneumothorax. It occurs before the side is distended. Furthermore, the return of the heart to normal position is the best indication of a complete cure. It is not rotated but is pushed to the normal side, its axis being practically unchanged. The dislocation of the heart is so extreme that years ago it was explained as a congenital deformity. The heart may lie entirely to the right of the mid-line in a left-sided case, while in a right-sided case the point of maximum impulse may even be three inches to the left of the left maxillary line.

Palpation.—The increase in size of the thorax, and the decrease in motility on respiration may be determined by palpation. Vocal fremitus is usually entirely absent over a pneumothorax.

Percussion.—The percussion note over a pneumothorax will be more or less hyperresonant, *i.e.*, full and drum-like. This change in quality of the note may not be marked and, therefore, it is a common mistake in the examination of a case of pneumothorax for the clinician to accept this hyperresonant note as the normal note and to consider the resonance of the normal side as impaired. Hyperresonance extending beyond the limit of the normal lung is an important early sign of pneumothorax. But sometimes the note over a pneumothorax is reported as dull. This may be due to an effusion in cases of hydropneumothorax or of pyopneumothorax, or to a marked thickening of the pleura (and yet in those cases reported by the author, which showed at autopsy the most thickening of the pleura, the note was even more drum-like than it was in the others) while in other cases the reason for the dulness is difficult to assign.

The percussion note over the area of fluid in cases of hydropneumothorax is by no means always dull. Indeed, it is very difficult to determine by percussion the level of the fluid. To determine the amount of fluid in this disease Skoda doubled the height of the apparent zone of dulness on percussion. The chest in these cases may hold surprising amounts of fluid, because, for one reason, the upper surface of the diaphragm may be depressed, or it may even present a concavity. This would make room for quite a large amount of fluid.

Movable dulness is marked in hydropneumothorax and in pyopneumothorax. The upper level of dulness may rise even three interspaces when the patient sits up. This is valuable as a diagnostic point, since this fluid is free to move on change of posture, while in hydrothorax it is not.

Saussier's sign in right-sided cases without fluid may be of value. To demonstrate this, one percusses sharply over the right eighth rib. If pneumothorax is present one can feel the rib pass over an air-space and then impinge against the liver.

Auscultation.—Early in a case of spontaneous pneumothorax the breath sounds are very distant or even inaudible, except, perhaps, over that part of the chest-wall which is very near to the lung, *i.e.*, in the back near the spine. Silence on auscultation, absence of vocal fremitus, and hyperresonance on percussion is a triad of signs almost pathognomonic of simple recent pneumothorax. But such conditions are best found in cases in which the lung and chest-wall are nearly normal. In the majority of cases the breath sounds have a remarkable blowing quality, in others they have a still more remarkable amphoric quality. These qualities are independent of the intensity of the sounds. Those with blowing quality resemble intense tracheal breathing, while the amphoric sounds frequently have an unusually loud, but always a musical, ringing quality. This may be true of the breath, the voice and the heart sounds. On one examination this quality may be absent, and later it may be present to a striking degree. One can understand this better if one remembers the relationship between the resonance cavity of a pipe-organ and the uninteresting rustle produced by its reed. The chest is the large resonance cavity, since the lung is partially collapsed against the spine. When the proper relationship obtains between the exciting sound in the lung and the resonance cavity, most beautiful amphoric phenomena are produced.

(*a*) *Amphoric Respiration.*—In many cases the breath sounds in pneumothorax resemble those produced by blowing across the mouth of an empty decanter. Breath sounds with such an amphoric quality were formerly supposed to be produced by the air rushing from the lung into the pleural cavity. It was therefore considered as evidence of an open fistula. It later became evident that it could be present in cases in which the fistula was known to be closed. It is now believed that these amphoric breath sounds are ordinary breath sounds very much modified in quality by a pneumothorax cavity acting as a resonance chamber. Marais held that the tension of the gas within the pleural cavity was of importance in producing this quality of sound. This is very probable, since an increased pressure would compress the lung and, therefore, alter its sound-producing and transmitting qualities. This may well explain, also, the occasional amphoric quality of the breath sounds on deep but not on quiet respiration; it may also be the reason why expiration only is sometimes amphoric, while inspiration is loud and blowing (since the tension is highest during expiration). It may explain, as well, the disappearance of amphoric sounds before death, when the respiratory motions are more feeble. Furthermore, it would well explain the appearance of amphoric respiration three or four days after the onset of a pneumothorax, *i. e.*, after the pulmonary excursions have become more forcible. Granting, however, that an open fistula is not necessary in the production of amphoric sounds, it is nevertheless true that a fistula, if open, will tend to assist in their production, especially in those cases in which the amphoric phenomena are heard only over certain areas of the chest-wall.

Similar sounds with amphoric quality can be heard over a distended stomach or bowel, in which cases the presence of fistula is, of course, not to be considered. They can also be heard over large tuberculous cavities, although some writers make a distinction between cavernous respiration and amphoric respiration. A cavity may, however, be large enough to produce the latter.

It is certain that the amphoric quality of breath sounds bears no relation to their intensity. The faintest murmur audible may be amphoric, and loud breath sounds may be simply blowing in quality.

In conclusion, therefore, it should be said that for the production of amphoric breathing, the condition of the lung in which the sound originated, and the importance of the pneumothorax cavity as a resonance cavity must be emphasized. When the conditions of resonance are satisfactory, beautiful amphoric breathing may be heard, whether the sounds are faint or loud. Any sound produced in the lung, whether in the bronchi or in a tuberculous cavity or through a bronchopleural fistula, may have amphoric qualities. This depends upon the pneumothorax cavity. In general, the more normal the pleural cavity, the less it is adapted to the production of amphoric sounds; and the more thickened the pleura, the more frequent are these sounds. (In a series of 10 cases produced by accidents of aspiration, the amphoric phenomena were practically absent.)

Cases with amphoric heart sounds are very rare, probably because the heart sound itself is of such a quality that the pneumothorax cavity cannot serve as a suitable resonance chamber. In some cases, however, the proper relationship has obtained, for in one case reported by Cornil the heart sounds were audible even to the bystanders.

(*b*) *Coin Sound.*—The coin sound as introduced by Trousseau is produced as follows: An assistant holds a silver dollar tightly against the front of the patient's chest and raps it sharply with the edge of another coin, the examiner meanwhile applying his ear to the patient's back. In a case of pneumothorax the sound produced is not only loud and close to the ear, but has a beautiful amphoric ring, so intense that it actually hurts. This sign may be present also over a large tuberculous cavity.

(*c*) *Metallic Tinkling.*—Those sounds which are termed "metallic tinkling" are so characteristic and so beautiful that, once heard, they cannot be forgotten or mistaken for anything else. Laennec states that they resemble the note made by striking a glass with a thin wire. They are also said to resemble a distant church bell. They are produced by respiration, by speaking or by coughing. At first they were supposed to be due to the bursting of the bubbles of air which enter the pleural cavity from a bronchopleural fistula which opened beneath the surface of the fluid. However, just as beautiful tinkling sounds may be heard when there is no free fluid in the chest and no open fistula. At present it is held that they may be produced by any fine, moist râles within the lung, provided the pleural cavity can act as a suitable resonance chamber. In some cases these sounds have been so loud that they were distinctly audible to the patient, while, in one case mentioned by Aubert, the metallic clinking could be heard in all parts of a large room. Metallic tinkling has been heard in other conditions, e.g., in the case of a large tuberculous cavity and of a renal cyst containing both air and fluid.

In conclusion, metallic tinkling is produced by any short, high-pitched sound produced in the lung near a suitable resonance chamber.

This sound may be a mucous râle, or it may be the bursting of a bubble, or the falling of a drop of fluid from the wall of the pleural cavity down into the fluid.

(*d*) *Succussion Splash.*—The succussion splash described by Hippocrates as occurring in "empyema" is incorrectly called "Hippocratic succussion," since succussion is the act of shaking the chest, and not the resulting splash. This splash is a valuable sign in determining the combined presence of fluid and air in any large cavity of the body. It is often an early sign of fluid developing in a pure pneumothorax before other signs of fluid can be detected. It can generally be heard if the ear is applied to the patient's back just over the pneumothorax cavity, while some one else gives the shoulders of the patient a quick shake. In some conditions, however, the splash may be so loud that it can be heard even throughout a large amphitheater. It may be produced also in patients with very large tuberculous cavities and sometimes in those with dilated stomachs.

LABORATORY FINDINGS.—The conditions present in the blood, urine, etc., will depend upon the primary disease in the lung and upon the exudate in the pleura.

The pleural exudate of hydropneumothorax is similar to that of pleurisy with effusion; and that of pyopneumothorax is similar to that of empyema. It is remarkable how seldom in these cases a serous fluid becomes purulent or a purulent one becomes fetid, although one would suppose that secondary infections through the fistula would be the rule. The fluid in cases due to external wounds is nearly always purulent. In the purulent effusions a great number and a great variety of organisms are found, the presence of air undoubtedly aiding in their growth. Some gas-producers may be able to provide the air which makes a case of empyema one of pneumothorax, while the organisms of gangrene, when present, produce their characteristic odor. In children, pyopneumothorax is more common than in adults.

Hemopneumothorax is not rare and develops especially in posttraumatic cases (stab wounds, bullet wounds, fractured ribs) and in cases due to the rupture of an emphysematous bleb.

Whatever mixture of oxygen, carbon dioxid and nitrogen is introduced into the chest, it soon becomes practically the gas of capillary blood: carbon dioxid 13.5 per cent., oxygen 14.4 per cent., nitrogen, 72.1 per cent. After death the amount of carbon dioxid increases even to 30.9 per cent., and this doubtless explains the gas which hisses out of the chest at autopsy.

ROENTGENOLOGICAL EXAMINATION.—The *x*-ray plates are very valuable in the diagnosis of the various forms of pneumothorax. Ofter this is the only means by which the presence of a circumscribed pneumothorax can be verified. In this way it is possible to exclude huge tuberculous cavities of the lung and diaphragmatic herniæ. The lung can thus be located in cases in which it is attached to the chest-wall and the presence of fluid can be determined, and its amount estimated.

Diagnosis.—The diagnosis of pneumothorax presents several problems. Among these are: Is there air in the chest? Is fluid present also? If so, what is the nature of the fluid? What is the condition of the lung? Is the fistula open, valvular or closed?

In a case of spontaneous pneumothorax the problem is not difficult. The onset is always sudden and severe, the chest is distended and hyperresonant, the limits of hyperresonance extending beyond the limits of the normal lung, the heart is much dislocated, the diaphragm is low, vocal fremitus is absent, and the heart sounds are absent, distant and sometimes peculiarly blowing or amphoric. The coin sound is present and metallic tinkling may be heard, provided one listens patiently over the entire chest. It may be practically impossible to differentiate diaphragmatic hernia without the *x*-ray examination, since practically all the signs of simple pneumothorax may be present. The chronicity (*i.e.*, permanency) of the condition, and the absence of any signs of pulmonary disease or of pleural exudate, should arouse suspicion. The author reported one case of this character as pneumothorax. The error was corrected only at autopsy. Huge tuberculous cavities may so simulate pneumothorax that a correct diagnosis is very difficult, especially in those cases in which much of the lung is reduced to a shell of pleura and is adherent to the chest-wall. The history of the case indicating extensive excavation of the lung, and especially the roentgenological findings, will be of great assistance in interpreting these cases. The succussion splash and many of the amphoric phenomena may also be present.

In pneumothorax due to an unsuspected tuberculosis the onset and physical signs will be those mentioned above, but the fever and signs of lung involvement will soon appear as the case progresses. In the absence of definite evidence of lung involvement, the tuberculin reaction may be used to differentiate tuberculous from spontaneous pneumothorax. The value of this test will depend entirely upon one's evaluation of this reaction. If the case is one of extensive pulmonary tuberculosis, the diagnosis is difficult, since the onset may be unnoticed and the condition limited because of the inability of the more or less solid and adherent lung to collapse. In these cases the *x*-ray plates may be necessary. Fluid is usually present, and as a consequence, the Hippocratic splash is also heard. In these cases the amphoric phenomena and the coin sound are usually present. The cases of tuberculosis with huge pulmonary cavities which occupy nearly the entire lung are mentioned on page 635. The Hippocratic splash on succussion, the coin sound, the amphoric phenomena, the metallic tinkling (especially), altogether, are quite conclusive of pneumothorax, but each of these alone is sometimes present in huge lung cavities, in diaphragmatic herniæ, in cysts of the kidney, and in cases with dilated stomach or colon. To determine the character of the effusion there should be no hesitation in making an exploratory puncture. To determine whether or not the fistula is open or closed, some writers have recommended the analysis of a specimen of the gas, but the author's experience would indicate that this is of little value.

Complications.—In the various forms of pneumothorax may be found all the various complications of the underlying lung conditions (tuberculosis, abscess, bronchiectasis, etc.), all the complications of pleurisy with effusion, of empyema, and of hemothorax. In addition, certain complications, such as subcutaneous emphysema, should be mentioned.

Sequelæ.—The sequelæ of the various forms of pneumothorax are the same as those of pleurisy with effusion and of empyema. A chronic pyopneumothorax, in which spontaneous cure is impossible, with fibrosis of the collapsed lung and thickened pleura preventing expansion, is a condition to be dreaded.

Association with Other Diseases.—Among the pulmonary diseases associated with pneumothorax in its several forms are:

EMPHYSEMA.—Pulmonary emphysema has from the first been considered an important cause of pneumothorax. This condition may be associated with extensive general emphysema, the bullæ varying in size from that of a pea to that of a pigeon's egg, or with traumatic interstitial emphysema, or with localized pleural blister resulting from the latter or occurring in connection with the contracting scar of a healed tuberculous area. Associated with these forms of emphysema simple spontaneous pneumothorax or hemopneumothorax may develop. The frequent presence of hemopneumothorax is doubtless due to the tear in a pleura in which circulation is still intact. In one of the author's cases, a woman twenty-two years old, with asthma since one year of age, and extreme emphysema, there was, for months at least, a condition of chronic partial pneumothorax in one chest.

PULMONARY TUBERCULOSIS.—Since the discoveries of Laennec it has been known that by far the majority of the cases of pneumothorax, over 90 per cent., are associated with tuberculosis. Galliard[20] ascertained that of all cases of tuberculosis under treatment simultaneously in all the hospitals of France, 1.054 per cent. had pneumothorax. Pathologists report that pneumothorax is present in 5 per cent. of all fatal cases of tuberculosis.[21] It occurs especially in the acute cases of tuberculosis and practically never in afebrile ones. If all cases in which pleural adhesions are important in the production of pneumothorax are classed as tuberculous, then many of the spontaneous cases also belong indirectly in this group and tuberculosis would explain much more than 90 per cent. of all cases. There is a tendency toward the development of pneumothorax in every case of tuberculosis, but this is prevented by the obliterative pleurisy which precedes a slow subpleural necrosis. For this reason, a perforation of the lung at the apex is exceedingly rare. Pneumothorax in cases of tuberculosis, is usually partial, owing to old adhesions, and it is often definitely circumscribed. Other cases of pneumothorax are due to adhesions resulting from a healed tuberculosis which may later cause a tear in the pleura, to the acute, small, rapidly softening subpleural cavities, so small that they are overlooked at autopsy, and to extensive subpleural cavity formation.

BRONCHOPNEUMONIA.—In the streptococcus bronchopneumonia epidemic which complicated the influenza of 1918-19, the cough was, in some cases, unusually severe, and rupture of the lungs was not rare. This in turn led to subcutaneous emphysema in 11 out of 1,701 cases reported by Berkley and Coffen,[22] while in 2 of these 11 cases a pneumothorax also developed.

PULMONARY ABSCESS.—These cases, prior to the epidemic of influenza in 1918-19, were exceedingly rare. Only one clear case due to a metastatic abscess could be found in literature.[18] The author believes, however, that many cases of pneumothorax which developed in the above-mentioned epidemic belong to this group.

BRONCHIECTASIS.—It is remarkable that so few cases of pneumothorax associated with bronchiectasis have been reported (only 13 up to 1920). The probability is that in bronchiectasis rapidly softening lesions are rare, and, as a result, the chronic inflammatory processes are rapid enough to protect the pleural cavity.

GANGRENE OF THE LUNG.—Gangrene of the lung, especially that following pulmonary embolism and thrombosis, may be important in the production of pneumothorax. In the few cases of bronchiectasis mentioned above, it was gangrene which weakened the wall of the cavity and allowed it to rupture.

PULMONARY EMBOLUS AND THROMBOSIS.—These conditions have been reported as causes of pneumothorax, and yet a secondary gangrene would seem necessary for the production of this complication.

Among the *pleural* diseases which lead to pneumothorax are:

(1) Adhesive non-tuberculous pleurisy in which the adhesions may later lead to pleural tear.

(2) Pleurisy with effusion and later pneumothorax, due to the following lesions: (*a*) a tear of the pleura, (*b*) rupture of a tuberculous vomica, (*c*) an accident occurring during exploratory puncture, such as when the needle cuts the visceral pleura, or (*d*) a mistake in aspiration, *e.g.*, when Potain's syringe is so attached that it pumps air into the chest instead of creating a vacuum in the bottle.

(3) Empyema and secondary pneumothorax due to necrosis of the lung or to the development of gas by gas-producing bacilli in the fluid.

(4) Cancer of the esophagus.

Clinical Varieties.—In simple or pure pneumothorax there is air only in the pleural cavity.

Spontaneous pneumothorax (tuberculosis excluded) develops suddenly and unexpectedly.

"Idiopathic" or "essential" pneumothorax are terms used as synonyms for the spontaneous type, while other writers use them in connection with cases due to the development of gas within the pleural cavity.

The term secondary pneumothorax indicates that the condition is clearly a complication of an intrapulmonary disease, especially tuberculosis, emphysema, abscess, bronchiectasis, etc.

External pneumothorax is due to a wound through the chest-wall.

The terms "open," "closed" and "valvular" pneumothorax are based upon the patency of the fistula through which air entered the cavity.

Pneumothorax acutissima is a form of valvular hydropneumothorax with rapidly rising intrapleural pressure leading to death unless relieved.

A pneumothorax may be double, if there is a pneumothorax cavity in each side of the chest, or if there are two cavities on the same side.

In cases of recurring pneumothorax the patient has more than one attack of this condition.

Pyopneumothorax necessitatis is a condition of pyopneumothorax which relieves itself by external rupture through the chest-wall.

Treatment.—In cases of simple pneumothorax the patient should be **quiet** in bed, and the cough should be controlled by **morphin** if necessary; this will also lessen the dyspnea. Some advise that the affected side of the chest be **strapped** in order that deep respiration may be avoided, and that the reïnflation of the lung and the danger of reopening the fistula may be prevented. There is some danger, however, of emphasizing this last consideration too much, for after all it is based chiefly on theory. The author believes, however, that there is a real advantage in strapping the affected side early, since this may in part prevent the progressive distention of the affected side. In the so-called suffocative cases (pneumothorax acutissima) simple **puncture** may help, but in most cases this is unnecessary and may do more harm than good. It has been found necessary to convert some so-called valvular cases into externally open ones by introducing a drainage tube into the chest and thereby preventing repeated inflation. The patient should be quiet until the heart has returned to its normal location. Otherwise the treatment is purely symptomatic.

The secondary cases should be treated for the underlying pulmonary disease, and the air disregarded unless its pressure reaches a dangerous degree, in which case simple puncture of the chest with a hollow needle will give great relief. But this is seldom necessary.

A hemopneumothorax should, if possible, be left severely alone.

Hydropneumothorax and pyopneumothorax should be treated like hydrothorax and empyema, except that in aspirating the former, care should be taken to drain slowly, for the negative pressure created may open anew the fistula and also suck some infectious matter from the lung into the pleural cavity. If the pleural exudate is pus it should at once be thoroughly **drained** and the cavity should be kept open by the resection of a rib. The author believes that far too great conservation has been taught in the treatment of cases of pyopneumothorax. Surely the ultimate prognosis of the cases would be more favorable if we operated and drained immediately, as soon as it is determined that the fluid is pus. The earlier the operation and the freer the drainage, the more rapidly will the fistula close and the less danger will there be of the terrible, permanent pneumothorax cavity. In a chronic case with little hope of reëxpansion of the lung, an extensive operation is justified; all the ribs, if necessary, should be resected in front and behind, and the cavity thus obliterated.

Prognosis.—The prognosis in spontaneous pneumothorax, with the exception of certain rare suffocative cases which were reported as being rapidly fatal, is usually favorable. The immediate mortality is about 2 per cent. (Furrell and Riesman.) The air alone will not infect the pleura or cause any reaction. It will disappear in from four to six weeks. And yet there is good reason to fear that the condition may recur even more than once, for it has done so in 12 per cent. of the cases.

The present popularity of artificial pneumothorax as the treatment of certain cases of pulmonary tuberculosis might lead to the belief that this condition as a complication of tuberculosis need not be dreaded. And yet as a spontaneous complication of tuberculosis it certainly renders the prognosis much graver, perhaps in part since there is generally also a complicating hydrothorax or pyothorax. West reported that the general mortality in cases of tuberculosis complicated by some form of pneumothorax was 70 per cent. Sixty per cent. of the patients died during the first month. Twenty-five per cent. died the first day. West estimates that not over 10 per cent. completely recover. Surely clinical experience was not the argument which led men to choose artificial pneumothorax as a therapeutic measure in tuberculosis.

The prognosis of chronic pyopneumothorax is not favorable unless the cases can be relieved somewhat by operation, although some of these patients have lived for several years.

Pathology.—No autopsies have been reported on cases of spontaneous pneumothorax, yet some examiners have incidentally found, in cases of healed tuberculosis, small pleural blebs, some the size of the end of the finger, on the edge of a tuberculous scar and directly connecting with a bronchus. The pleura which forms this tiny balloon is so thin that it is almost transparent, probably as a result of long-continued malnutrition. One may easily believe that a sudden and even insignificant rise of intrabronchial pressure would finally rupture this shell.

In the cases of tuberculous pneumothorax one finds, in addition to all the lesions of chronic tuberculosis, early acute lesions and often a small subpleural cavity, which has ruptured. The most common situations of the perforation are the inferior portion of the upper lobe and the superior portion of the middle and lower lobes. It is often near a mass of old adhesions. The perforation, as seen at autopsy, may vary in size from that of a pin-prick, located only by inflating the lung under water, to a fistula 3 cm. in diameter. The two lungs are affected with equal frequency. In one of the cases reported by the author there were at autopsy two circumscribed pneumothorax cavities on the same side, the upper opening into the esophagus. In some cases the lung is almost riddled with cavities and almost airless from disease, and yet the pneumothorax seems to have arisen from a small, superficial acute lesion. In 18 tuberculous cases with pneumothorax which the author reported, there were at autopsy no pleural effusion in 3, pus in 14, and serous fluid in 1. An old autopsy test for pneumothorax consisted in puncturing the chest-wall and holding a lighted candle to the wound, in which case the flame was sometimes blown out; or a better test consisted in dissecting back the anterior chest-wall in all directions from the median incision, filling the resulting shallow cavity with water, and then plunging a knife through the water into the pleural cavity and noting whether or not air bubbled out. There is good evidence that the high pressure of the gas found at autopsy develops in part at least after death.

In the cases of bronchiectasis with pneumothorax the cavity was large and the wall had ruptured near the adhesions.

Hydrothorax

Hydrothorax, or a collection of serous fluid in the pleural cavities, occurs to a greater or lesser degree in all dropsy-producing diseases, and in cardiac and renal diseases, often when a general edema is not pronounced. It is in the last two conditions only that the fluid collects in amounts sufficient to be of importance clinically and its presence in considerable amount in renal disease is often due to the accompanying cardiac complications. When small in volume this fluid may give rise to few or no symptoms, and, as a rule, even when large in amount, its presence is overlooked, since its symptoms are masked by those of the far more important conditions present. As a general rule the pleura should be examined for hydrothorax in all cases of heart or renal disease, especially in those with severe dyspnea. Far too many massive effusions are first found by the pathologist at the autopsy table. These cannot all be explained as antemortem events.

The formation of an hydrothorax itself is not attended by fever, pain or many of the symptoms of pleurisy with effusion. However, cough and sputum are usually present, due, if to nothing else, to edema of the lungs caused by the embarrassed pulmonary circulation. The physical signs are identical with those of an inflammatory exudate, except that no friction rub is heard. The effusion is practically always bilateral and may be almost equal in the two sides of the chest, but this is rare, for in the great majority of cases there is so much more in the right chest than in the left that clinically the effusion is unilateral. Combining the figures of Stengel and of Lord (57 cases), the cardiac hydrothorax was bilateral in 25 cases but greater in the right pleural sac in 15 of these, unilateral and right-sided in 21 cases, and left-sided in only 7 (in 2 others the right pleural cavity had been previously obliterated). Thus the fluid was confined to or predominated on the right side in 36 out of 57 cases (63.1 per cent.).

The fluid itself is yellow, clear, and free from fibrin flocculi. It may often contain red blood-cells. It clots slowly or not at all, unless a little blood is added. Its specific gravity in cases due to cardiac decompensation ranges from 1.010 to 1.015, and the albumin from 1 per cent. to 3 per cent., while in cases of general anasarca the specific gravity is 1.010 or below, and the albumin ranges from a trace to 1 per cent. In both cases the endothelial leukocytes predominate except in the early cases in which for a time there may be a preponderance of lymphocytes.

Etiology.—The very use of the terms transudate and "non-inflammatory exudate" is evidence of a widespread belief that the mechanism which produces an hydrothorax differs essentially from that which produces an inflammatory exudate. A transudate, although the fluid is by no means blood-plasma, is supposed by many to be the result of some sort of mechanical process, *e.g.*, a filtration of blood-plasma due to increased venous pressure which dams back the blood into the pleural capillary bed. In cases of chronic passive congestion due to heart disease, there may be some ground for this belief, but not much, while in renal cases there is often none.

There will be an increase in the pleural fluid in all cases of general anasarca, whatever the cause, yet amounts sufficient to be of importance clinically are due to renal or cardiac disease, to the pressure of a local tumor in the chest or near enough to it to disturb the pleural circulation, or to pressure on the azygos vein or a possible thrombosis of this vein. There is some question as to whether or not renal anasarca alone can cause a massive hydrothorax. The weight of evidence on this point is in favor of the importance, in these conditions, of a secondary cardiac or other circulatory disturbance. And yet, that the mechanical element is important is evident from the great predominance of fluid in the right thorax. Stengel attributed the predominance of the fluid on the right side in cardiac and renal cases to compression of the azygos veins, while Fetterhold and Landis claim that it is due to the partial occlusion of a pulmonary vein, caused by the pressure exerted upon it by the dilated right auricle. If the patient lies on one side much of the time, there will be a tendency for the fluid to predominate on that side. Notwithstanding all the evidence in favor of the mechanical factors in the production of hydrothorax, since the early days of pathology it has been claimed that one must assume some pathological process in the walls of the capillaries themselves to explain edema, as well as hydrothorax and hydroperitoneum. In renal cases this is very reasonable, since the effusion is not as equally distributed over the body, as one might expect if mechanical forces alone determine its presence.

Complications.—The transudate may assume such volume that the lungs are compressed and the heart itself is embarrassed, in which case there will be much interference with respiration and circulation.

Edema of the lung is not rare in cases of hydrothorax. This may be due in small part at least to the presence of the transudate, but the chief cause of the edema will be the same as that of the transudate.

Association with Other Diseases.—Hydrothorax of greater or lesser volume will be present in all dropsy-producing diseases, but a volume sufficient to attract attention clinically is seen only in connection with general dropsy, either cardiac dropsy, as in mitral disease, renal dropsy, as in subacute parenchymatous nephritis, or in hemic dropsy.

Treatment.—The treatment deals primarily with the underlying condition, especially the heart and kidney disease. In addition, free **purgation** and a **dry diet** will have more influence over the volume of the transudate than over that of the exudate of the pleurisy with effusion.

Prognosis.—The prognosis in general is that of the underlying disease, although the effusion itself may be sufficient in volume to cause death unless it is removed.

Pathology.—The pleural surfaces in cases of hydrothorax are often smooth and free from all evidences of inflammation; in other cases they are slightly cloudy and swollen.

HEMOTHORAX

Definition.—By hemothorax is meant the presence of pure blood in a normal pleural cavity. This is to be distinguished sharply from hemorrhagic pleurisy, since in hemothorax the pleura itself is normal at the onset, and serves merely as a receptacle for the blood.

Etiology.—Hemothorax may be the result of the rupture of an aneurysm of the arch of the aorta, or it may be due to the pressure of a tumor on the thoracic veins, or to a trauma rupturing or cutting the intercostal arteries, or other blood-vessels in direct proximity with the pleural cavity.

Symptomatology.—The signs of hemothorax are dulness to flatness on percussion, strong voice conduction and a very dense shadow on roentgenological examination, much denser than that of a pleural effusion.

CHYLOTHORAX

Definition.—Fluids which are milky in appearance because of a high fat content are called chylous fluids. These are evidently due to lesions of the thoracic duct or of its radicals. Those fluids the milky appearance of which is due to large numbers of cells undergoing fatty degeneration, are termed chyliform. This distinction has, however, proven of little practical value, for the difference between these two kinds of fluid seems to be one of degree rather than of kind. These effusions are rare.

Etiology.—It has been reported that chylothorax with chylous fluid in the pleural cavity is the result of trauma in 30 per cent. of the cases; of cancer of the pleura in 18 per cent.; of occlusion of the left subclavian vein in 15 per cent.; of compression of the thoracic duct in 7 per cent.; of sclerosis of lymph-vessels in 7 per cent.; of lymphangiectasis in 7 per cent., and of malignant lymphoma and blood parasites (probably filaria) in 16 per cent.

Of the cases with chyliform effusion 38 per cent. were the result of cancer of the pleura, of cancer involving the lymph-vessels, etc., tuberculous pleurisy, and of amyloid diseases of the pleural blood-vessels. Lewin [23] has presented the best review of this subject.

Symptomatology.—Chylous effusions have been found in patients of all ages and in one or both pleural sacs. These fluids are milky-red (from the mixture of blood), yellow, or green in appearance, odorless or with a slightly sweetish odor. They may resemble pus in appearance. If they are allowed to stand, a definite cream may rise. The emulsion of the fat cannot be cleared by filtration or by centrifugalization, but it will disappear if the fluid is shaken out with ether. Chemical analyses have shown the following:

Fat, 0.06 per cent. to 3.71 per cent.
Albumin, 3.36 per cent to 7.37 per cent.
Total solids, 5 per cent. to 10 per cent.
Organic matter, 1 per cent.

Casein and fibrin have been found, as well as cholesterin and lecithin. Glucose may be present in about the frequency and quantity in which it is present in clear serous effusions. If more than 0.2 per cent. is present, however, this may indicate that the thoracic duct is the source of the effusion. Microscopical examination shows the fat in fine emulsion and (in the chyliform cases especially) it shows degenerating cells in great numbers.

Pseudochylous fluids are practically fat-free and owe their milky appearance to some unknown albuminous body (some say it is a compound of globulin and lecithin). If they are allowed to stand, these fluids remain homogeneously milky.

Diagnosis.—The recognition of the chylous and chyliform fluids may depend upon chemical and microscopical analysis, since some fluids may easily be mistaken for pus. Pleural fluid of this character may be suspected in cases of polyserositis, if the ascitic fluid is chylous. It is to be suspected as a sequence to trauma, to thrombosis of the left subclavian vein, or to malignant disease of the pleura.

Treatment.—Aspiration should be delayed unless the amount of effusion is serious, since the creation of negative pressure in the chest would further escape of chyle from wounded lymph-vessels. The patient must be kept quiet until the wounded vessels have had time to close.

Prognosis.—The prognosis is usually grave since the underlying diseases are usually serious, yet in an increasingly large number of cases of unknown origin the patients have recovered. Pisek [24] reported a case of true chylothorax, cause unknown, in a two-months-old infant. The child recovered. In the traumatic cases the prognosis is favorable.

PLEUROMYCOSES

ACTINOMYCOSIS OF THE PLEURA

Definition.—Actinomycetic infection of the pleura is a chronic suppurative process produced by *Actinomyces bovis.*

Etiology.—Actinomycosis of the pleura is usually an extension of a pulmonary infection, but the original focus of infection may be a vertebra, an abdominal organ, or the esophagus. It is a slowly progressive infection which is characterized by the formation of several separate pockets of infection connected by burrowing sinuses, and by the display of little evidence of healing. Any organ may be invaded. The fistulæ are usually multiple.

Symptomatology.—CLINICAL HISTORY.—*Mode of Onset.*—In every case of empyema of the chest which presents atypical features, actinomycetic infection should be suspected. It should be suspected especially when an empyema is associated with chronic suppurative processes in the lung, with interstitial pneumonia, with pulmonary abscess or gangrene, and particularly if the pus ruptures externally.

Clinical Course.—The symptoms and signs are those of an encapsulated empyema which developed insidiously. The point of attack is usually situated at the base of the chest, is small in size, sluggish in growth, and advances by the formation of burrowing sinuses. The disease proceeds slowly and as a rule relentlessly, without regard to the tissue involved. Exploratory puncture will give pus in which sulphur granules can be seen microscopically. These vary in size from very minute bodies to granules as large as 2 mm. in diameter. They are white or yellow in color (hence the name "sulphur granule"), irregular in shape, and soft or even calcareous in texture. On microscopical examination it is found that these are composed of branching gram-positive filaments among which are masses of granules surrounded by filaments which radiate from the granular mass and the distal tips of which have evidently degenerated into club-shaped bodies.

In some cases an obliterative pleurisy will precede the extension of the disease, protecting the pleural cavity from invasion, while in others, in which the pleura itself is not actively invaded but in which it is in direct proximity to the disease, a fibrinous pleurisy, or a pleurisy with serous effusion, may complicate the case.

The *x*-ray examination is particularly valuable, since it will indicate the local character of the empyema; frequently it will also show the primary infection in lung, bone, etc.

Complications.—Actinomycosis is practically never limited to the pleural cavity, but spreads to neighboring organs, to the ribs, etc. It may perforate the chest-wall, especially in the lower thoracic zone. Amyloid degeneration of the various organs is a common result.

Treatment.—The treatment consists in the thorough **evacuation of the pus** and the administration of **potassium iodid** in large doses.

Prognosis.—The prognosis is very unfavorable, although a few cases would seem to have been arrested.

NOCARDIOSIS (STREPTOTHRICOSIS) OF THE PLEURA

A group of branching, acid-fast organisms somewhat resembling actinomycosis, and often called "streptothrix" may invade the pleura in

connection with the infection of neighboring organs. The lesions resemble those of tuberculosis.

TUMORS OF THE PLEURA

Carcinoma of the Pleura

The primary malignant tumors of the pleura are now all grouped as carcinomata, although frequently described as sarcomata, endotheliomata, etc. Histologically they resemble epithelial tumors, and indeed the histologists now classify the pleural endothelium as an epithelium. Therefore, endotheliomata will not be considered as a separate form of pleural tumor. Keiltz[25] has given a good report on one of these cases.

Etiology.—The disease is most common between the ages of forty and fifty years, and is especially prevalent in men. The most common symptoms are progressive loss of weight, dyspnea, and fluid in the pleural cavity.

Symptomatology.—The disease is usually mistaken at first for a pleurisy with effusion (especially tuberculous), although fever is seldom present. Pain is often experienced, and is increased by deep breathing. The patient complains of progressive loss of weight and strength, of cough, of dyspnea and even of orthopnea (especially if the almost constantly present pleural effusion is considerable in amount). If, as is sooner or later the case, the cancer invades the lung, cough with bloody sputum is the rule. The thoracic distress is greater than one would expect in a case of simple pleurisy.

Physical Findings.—The physical signs are those of pleurisy with effusion, together with marked thickening of the pleura, and later consolidation of the lung. The affected side is at first larger than normal; then it becomes progressively more contracted. The fluid accumulates rapidly, but it does not dominate the picture as it does in pleurisy with effusion. There is even greater limitation of motion on respiration than there is in pleurisy; there is a more fixed heart, and less collapse of the lung, all of which is due to the greater thickening of the pleura and to the invasion of the lung.

Laboratory Findings.—The pleural fluid is serous at first, and would possibly remain so if it were not tapped; later it becomes bloodstained, or hemorrhagic, or stained by old blood, and, therefore, is of a chocolate color. The content of the blood seems to depend upon the amount of aspiration employed. Superficial blood-vessels on the infiltrated pleura may be ruptured by the negative pressure created by the aspiration. The specific gravity of the pleural effusion in these cases is 1.018 or less.

Microscopical examination reveals a predominance of epithelial cells in the fluid, many of which are in clusters of proliferating cells called "mulberry masses." Some find the large numbers of these cells with nuclei in mitosis an aid to diagnosis. In several cases the small plug of tissue, which is removed from the lumen of the aspiratory needle in a dry tap, will prove on section to be malignant tissue (Steiner).

Diagnosis.—In any case of effusion in the pleural cavity without fever and with loss of weight and strength, malignant disease of the pleura should be suspected. The negative tuberculin reaction and the absence of tuberculosis elsewhere in the body will help to exclude such disease. Metastases in the neighboring glands and at a point of previous puncture are of value. The skiagrams of the chest are of great value.

Treatment.—The pleural fluid should be removed in small amounts and at frequent intervals, if too much discomfort is not experienced. The early removal of much fluid may be justified, but later, after the lung and pleura have lost much of their elasticity, this will increase the pain as well as the hemorrhage. Morphin should be freely used.

Prognosis.—Few patients live over two years after the onset of the symptoms.

Under the diagnosis "primary endotheliomata of the pleura," Keiltz found 9 cases among 5,000 in the records of the McManes Laboratory of Pathology, University of Pennsylvania, and quotes Clarkson as stating that there were only 2 in 10,000 autopsies at the Pathological Institute at Münich. He was able to collect only 41 cases from the literature.

The growth appears as one large mass, usually posterior in position, infiltrating the lung, or as several small nodules, confined to and scattered over the pleura. Metastases are common but not widespread, although the cases which Keiltz reported had widespread metastases.

Primary Sarcoma of the Pleura

The symptoms of sarcoma of the pleura are very similar to those of primary carcinoma. An effusion will usually be present, which is generally hemorrhagic, at least after the chest has been once tapped. On microscopical examination of the sediment the discovery of spindle-cells may suggest the diagnosis. This disease is uncommon; not over 24 cases have as yet been reported.

The tumor is usually a single mass of very variable size, sometimes even the size of a man's head. In some cases there are multiple masses, or a diffuse growth resembling epithelioma. Various neighboring organs may be involved by extension, and others by metastasis. Microscopically the tumors described are small, round-celled sarcomata, spindle-celled sarcomata, fibrosarcomata, and myosarcomata.

Secondary Malignant Tumors

The majority of malignant tumors of the pleura are secondary to those of the lung, mediastinum or chest-wall, while others are metastases from any distant organ. These tumors are as a rule small, separate nodules. The pleural fluid in such cases may be serous, but it is generally bloody.

ECHINOCOCCUS DISEASE OF THE PLEURA

Etiology.—*Tænia echinococcus* is a small tapeworm, the usual host of which is the dog. The shell of an egg ingested by man is dissolved in the stomach and the liberated embryo migrates through the wall of the stomach and is then carried by the blood or lymph stream to distant organs, including the pleura. The presence of more than one separate cyst indicates an originally multiple infection. The embryo encysts itself in the tissue and forms a small bladder, from the inner wall of which projects the head of the cestode armed with hooklets.

Symptomatology.—CLINICAL HISTORY.—Echinococcus cysts of the pleura are of slow development, since they require perhaps from six to twelve months to reach the size of the fist. The cysts in the pleura present few symptoms until they are fairly large, while even in some cases with large cysts the involvement of the pleura is so overshadowed by the symptoms of involvement of other organs that the pleural disease is overlooked. In uncomplicated cases fever is absent and loss of weight is uncommon.

In cases with an apparently solitary pleural cyst the symptoms and signs are those of a slowly growing thoracic tumor with progressively increasing dyspnea. Some cases have no cough, while others have a complicating bronchitis with cough and mucoid sputum. If a pleurisy develops, there will be pain on respiration. In a few cases such pain was present even when no pleurisy was evident.

PHYSICAL FINDINGS.—The physical signs are those of an encapsulated pleural exudate: localized prominence of the affected side, with diminished respiratory movements, flatness on percussion, with the line of dulness in some cases converging upward, loss of vocal fremitus over the dull area, and distant tubular breath-sounds. The liver, spleen and heart are displaced by a large cyst in their neighborhood.

LABORATORY FINDINGS.—Among the laboratory signs an eosinophilia of the blood stream has been observed.

In those cases in which the compressed lung develops a bronchitis the sputum is mucopurulent in character, while in those in which the cyst perforates through the lung and establishes a pleurobronchial fistula, the clear cyst fluid is expectorated and for a long time also the scolices, hooks and laminated fragments of cyst-wall.

Exploratory puncture of these cysts should never be attempted, since several deaths have been reported.

Diagnosis.—The demonstration of an echinococcus cyst in another region of the body suggests the diagnosis of an echinococcic disease of the pleura in the case of any patient who has also a doubtful pleural condition. The previous occupation (close association with dogs) of the patient may be of value. .

A positive diagnosis of hydatid pleural disease is possible only with the demonstration of characteristic cyst contents: scolices, hooklets or fragments of laminated cyst-wall. An acute urticarial rash following thoracocentesis is very suggestive. Specific antibodies in the blood of these patients may be demonstrated by the complement fixation test.

It is difficult, even impossible, to determine whether the cyst is primarily one of the pleura, of the lung or of the liver. An intrapulmonary cyst is more apt to cause pulmonary symptoms, such as cough, bloody sputum, etc., while dyspnea would be less marked and pain less common. The sub-diaphragmatic cysts are very difficult to differentiate. In these cases Litten's sign may persist, the excursion of the lower margin of the lung may be little disturbed and there may be no sign of lung involvement, while the fluoroscopic examination may decide the question.

Neoplasm of the lung may often be difficult to exclude. In these cases there will be greater disturbance of the general health, less sharply localized physical signs, and often some evidence of a primary disease or of metastasis of the tumor. In hydatid cysts of the pleura there will be a progressive enlargement of the chest rather than the later contraction so often seen in malignant disease. A localized encapsulated empyema may be excluded by the absence of any history of an acute onset and by the chronic course of the disease.

Complications.—The simple pleurisy and bronchitis due to the presence of the cyst are of little moment, but the rupture of the cyst through the lung leads to a bronchial fistula through which the cyst contents are slowly evacuated; this frequently leads to secondary infection of the lung, which causes septic pneumonia and pulmonary abscess or gangrene. Rupture of some cysts into the pleural cavity and of others externally through the chest-wall has been reported.

Rupture of the cyst may be spontaneous, or it may be the result of injury, or it may follow exertion. The patient is sometimes unconscious of the rupture, while on the other hand he may feel a sharp pain. If secondary pyogenic infection of the cyst has developed, the symptoms are those of a general infection. Rupture of the cyst is very apt to lead to urticaria and to the symptoms of mechanical suffocation or of severe intoxication: delirium, collapse, and death. If the disease of the pleura is due to the rupture into it of a cyst in the liver or other abdominal organ, this pleural cavity may then rupture through into the lung. The cyst itself sometimes becomes infected and then gives the symptoms of abscess or encapsulated empyema. Such infected cysts are especially apt to rupture.

Treatment.—If possible the **cyst** should be **removed** intact at operation; if this is not possible the cyst may be **evacuated,** freely **drained** and the cyst-wall later removed. Aspiration should not be attempted. Infected cysts should be treated like any abscess.

Prognosis.—All cases of pleural hydatid cysts or of parapleural cysts which have ruptured into the pleural cavity have resulted in death. The prognosis of those cysts which perforate into the lung is a little better. The cases treated surgically have reacted fairly well.

Pathology.—Echinococcus cysts are quite latent in their early development and often attain considerable size before they attract attention.

It is frequently quite impossible to determine the tissue in which this infection actually started. Echinococcus cysts are usually single sacs containing many daughter cysts (endogenous echinococcus). They are seldom multilocular from external budding (exogenous echinococcus). If the cyst has developed within the pleural cavity or in the tissues lining the pleural cavity, the case is one of pleural echinococcus. If it develops in an organ bordering the pleural cavity, it is one of a parapleural echinococcus. The cases of pleural echinococcus are rare, constituting only about 1.5 per cent. of all cases of echinococcus disease. The right pleura is involved more often than the left, and the lower thoracic zone is much more frequently involved than are the upper or middle zones.

The cyst grows slowly and steadily compresses the neighboring organs, but causes very little local reaction beyond the formation of a connective tissue capsule. Pleuritis is uncommon.

The rupture of the cyst is rare. A rupture may perforate through the lung into a bronchus, or externally through an intercostal space. Infection of the cyst cavity is more common and changes the cavity into an abscess.

Extension of the cestode infection by the rupture of the mother cyst, and the consequent liberation of the daughter cysts has never been proven for the pleural cases. Parapleural echinococcus disease of the lung, of the liver or diaphragm, and especially of the spleen, kidney, etc., may encroach upon the pleural cavity and give all the signs and symptoms of pleural echinococcus. In such cases the pleural cavity is usually obliterated by a preceding adhesive pleurisy, although the formation of serous and purulent effusions has been reported.

REFERENCES

1. Lord. Diseases of the Bronchi, Lungs and Pleura, 1915.
2. Capps. Arch. Int. Med., 1911, viii, 717.
   ——— Am. Jour. Med., March, 1916, cli, 333.
3. Kelly and Weiss. Jour. Med. Sc., Dec., 1918, clvi, 781.
4. Cetrangolo. Jour. Am. Med. Assn. (Abst.), May 31, 1918, p. 1651.
5. Greene. Jour. Med. Sc., March, 1906, cxxxi, No. 3, pp. 519-522.
6. Bine. Am. Jour. Med. Sc., 1918, clv, 579.
7. Petzetakis. Bull. et mém. Soc. méd. d. hôp. de Paris, 1918, 3rd Series, xlii, 487.
8. Lyter. Am. Jour. Med. Sc., Nov., 1918, clvi, 665.
9. Brooks and Cecil. Arch. Int. Med., Sept., 1918, xxii, 269.
10. Thomas. Jour. Am. Med. Assn., Jan. 4, 1919, lxxii, 28.
11. Schulman. Jour. Am. Med. Assn., April 28, 1917, lxviii, 1256.
12. Vaughan and Schnabel. Arch. Int. Med., Oct. 5, 1918, xxii, 440.
13. Beals, Zimmerman and Marlow. Jour. Infect. Dis., Nov., 1918, xxiii, 475.
14. Miller and Lusk. Jour. Am. Med. Assn., Aug. 31, 1918, lxxi, 702.
15. Ballin. Jour. Am. Med. Assn., Feb. 1, 1919, lxxii, 335.
16. Garbat. Jour. Am. Med. Assn., Feb. 1, 1919, lxxii, 330.
17. Sedgewick. Jour. Am. Med. Assn., July 21, 1917, lxix, 235.

18. Emerson. Johns Hopkins Hosp. Reports, xi, 1 (for reference to earlier literature).
19. Hamman. Am. Jour. Med. Sc., 1916, cli, 229.
20. Galliard. Bull. et mém. de la Soc. méd. d. hôp. de Paris, 1896, 3rd Series, xiii, 253.
21. West. Lancet, May 3, 1884.
22. Berkley and Coffen. Jour. Am. Med. Assn., Feb. 22, 1919, lxii, 535.
23. Lewin. Am. Jour. Med. Sc., 1916, clii, 71.
24. Pisek. Jour. Am. Med. Assn., July 28, 1917, lxix, 310.
25. Keilty. Am. Jour. Med. Sc., 1917, cliii, 888.

CHAPTER V

DISEASES OF THE BRONCHI

By Luther F. Warren, M.D.

Bronchitis, p. 659:—Definition, p. 659; Etiology, p. 659.
Acute bronchitis, p. 660:—Symptomatology, p. 660—Influenzal bronchitis, p. 661: —Symptomatology, p. 661—Capillary bronchitis, p. 662:—Definition, p. 662; Symptomatology, p. 662:—Physical signs, p. 663; Physical findings, p. 663; Laboratory findings, p. 664—Diagnosis, p. 665; Complications, p. 666; Clinical Varieties, p. 667; Treatment, p. 667; Pathology, p. 672; History, p. 673.
Chronic bronchitis, p. 674:—Etiology, p. 674; Symptomatology, p. 675; Diagnosis, p. 678; Special and associated clinical types, p. 678:—Bronchitis and heart disease, p. 678; Bronchitis and renal disease, p. 679; War bronchitis, p. 679; Special forms, p. 680:—Dry bronchitis of Laennac, p. 680; Serous bronchitis of Laennac, p. 680; Purulent bronchitis, p. 680—Treatment, p. 681; Pathology, p. 682.
Plastic bronchitis, p. 683:—Definition, p. 683; Etiology, p. 683; Symptomatology, p. 684; Diagnosis, p. 687; Association with other diseases, p. 688; Treatment, p. 688; Prognosis, p. 689; Pathology, p. 689.
Putrid bronchitis, p. 690:—Definition, p. 690; Symptomatology, p. 690; Course and complications, p. 691; Diagnosis, p. 691; Treatment, p. 692.
Tracheobronchial syphilis, p. 692:—Definition, p. 692; Symptomatology, p. 693; Diagnosis, p. 695; Associated lesions, p. 696; Treatment, p. 696; Prognosis, p. 697; Pathology, p. 698.
New growth of the bronchi, p. 698:—Definition, p. 698; Etiology, p. 699; Symptomatology, p. 699; Diagnosis, p. 702; Prognosis and Treatment, p. 703; Pathology, p. 703.

BRONCHITIS

Definition.—Bronchitis is an inflammation of the mucous membrane of the bronchial tubes. Although many types have been described it seems most practical for our purpose to limit our consideration to acute bronchitis, chronic bronchitis, plastic bronchitis, and putrid bronchitis. In acute bronchitis we plan to differentiate that type with involvement of the larger bronchi, or tracheobronchitis, from that involving the smaller bronchi and bronchioles, or capillary bronchitis. As influenzal bronchitis presents a clinical picture differing materially from that of the other forms of acute bronchitis we will discuss its clinical aspects separately.

Etiology.—Acute tracheobronchitis is one of the commonest diseases. Children as well as the aged are attacked frequently. Sixty per cent. of the author's cases have occurred in strong adult males, and most of these were seamen or men working along the water front who are unduly exposed to severe changes of weather. Most of the patients entered the hospital in the changeable weather of the fall or early spring, with a history of "catching cold," and this is the etiology of most cases of acute bronchitis except those occurring at the time of influenza epidemics.

Many other etiological factors which activate a more limited number of cases have been worked out by Hoffmann.[1] These he gives as dust and gas inhalation; specific infections from the surface of the mucous membrane as in whooping cough, erysipelas, diphtheritic and putrid bronchitis; nervous disturbances; constitutional diseases; infectious diseases, as in measles, small-pox, typhus, malaria, glanders, syphilis, tuberculosis, and recurrent intoxications; diseases of the upper air passages—pleura, mediastinum, thorax (scoliosis, kyphosis); diseases of the heart and blood-vessels; organs of digestion; kidneys; and diseases of the skin. When the bronchial mucous membrane has been irritated by any of the foregoing factors its resistance is diminished, and the organisms which are found normally in the trachea and bronchi increase their activity. Particularly is this true if there has been a chilling of the body which diminishes the general resistance of the individual.

Another etiological factor in the infectious group of bronchitis is exposure to other cases. Commonly the disease spreads from one to many persons by contact. This is especially applicable to the influenza group. The author's attention has been called especially to the etiology of epidemics in military life by Vaughan and Palmer[2], Soper[3], Emerson[4] and Zinsser[5], who all emphasize the importance of overcrowding, inadequate ventilation, exhausting drill, promiscuous coughing, sneezing, and spitting as causative factors.

ACUTE BRONCHITIS

Symptomatology.—COUGH.—This is the most common symptom the author has met in his series of 249 hospital cases of acute bronchitis in the past five years. It occurred in 85 per cent. of these cases in a sufficiently severe degree for the patients to complain of it. Probably it is present to some degree in all cases. It is a primary symptom of this condition. Many other symptoms are secondary to it, such as nausea, loss of appetite, vomiting, certain types of thoracic pain, sleepless nights, etc. It begins as a dry hacking cough, usually not distressing to the patient, and it commonly follows a history of exposure and "catching cold." Occasionally it begins with severe paroxysms and these continue throughout the course of the disease. Many patients may be but little disturbed by these attacks during the day but they recur incessantly during the night. After continuing from twenty-four to forty-eight hours the cough usually becomes associated with expectoration. This is at first mucous in character, has no odor, and gradually changes into a mucopurulent type. The color becomes yellowish or dirty greenish yellow, and rarely it is blood-streaked. The amount of sputum varies from a few cubic centimeters to as many ounces in twenty-four hours. Usually at the end of several days, or it may be two weeks, the cough and expectoration gradually decrease and disappear.

PAIN.—Chest pain is the second symptom of importance and of frequency in the author's series. It was noted in about the same percentage as was cough and was variously described. Many complained of a tickling sensation as of a feather beneath the upper sternum which commonly gave a sore or burning feeling on coughing. At times a tightness or pressure in the thorax was the feeling described and at other times the pain was sharp and stabbing in character, radiating to either side and made worse by coughing. Occasionally it appears on one side only, or it may be referred to the precordium; at other times to the back between the shoulders or to the epigastrium.

TEMPERATURE.—Although temperature was seldom complained of, it was found in 50 per cent. of the author's cases in the course of the illness. Its duration averaged about five and a half days. In the majority of cases it did not go above 101° F. (38.33° C.), but sometimes it was 102° F. (38.89° C.) and 103° F. (39.44° C.) at the onset. The course of the temperature was either a slowly decreasing one or showed daily remissions with the highest point reached in the afternoon hours.

HEADACHE.—This was not an uncommon symptom. It was present in 22 per cent. It was described either as constant or paroxysmal, and occurred most often over the frontal region. At times it was increased by coughing. Apparently sinus infection explained the frequency of this type. In uncomplicated cases this symptom disappeared within seventy-two hours.

Many other symptoms appeared in the author's series, but they occurred with more or less infrequency and do not stand out as having much clinical significance. Weakness and dyspnea each appeared in 52 of his cases, while sore throat and dizziness were complained of by 20 of his patients. Nausea and vomiting were occasionally observed and were most often associated with paroxysms of coughing. Chilly feelings and sweating were found to be less frequent than other authors have recorded.

Influenzal Bronchitis

Symptomatology.—Influenza is a disease entity; it may affect any portion of the respiratory mucous membrane. When the mucous membrane of the bronchi is the seat of infection a clinical picture is produced which differs rather markedly from that met with in other forms of acute bronchitis and hence seems worthy of emphasis. In this form cough is likewise always present and may be most severe, loud, barking in type, frequently occurring in paroxysms resembling whooping-cough. These paroxysms may be most distressing to the patient and are of such intensity as to be frequently accompanied by vomiting. Expectoration also differs from that seen in ordinary acute bronchitis on account of its frequent hemorrhagic character. The expectoration may be blood-streaked or even inclined to frank hemoptysis.

In addition to this type of cough and expectoration, headache, general body pains, and weakness were present in over half of the author's cases. The headache is most severe, usually constant, and commonly refractory to treatment. The body pains were described as aching or soreness deep in the muscles and bones. It may reach such a degree that the patient refrains even from moving about in bed. The weakness is often described as complete exhaustion or depletion to an extent not seen in other forms of acute bronchitis. The patients often say that they feel so weak that they cannot stand on their feet and do not care to take nourishment. Coryza, sore throat, vomiting, and epistaxis are also met with much more frequently in this type of infection than in the other forms of acute bronchitis.

Physical Findings.—The physical signs, as well, vary very much from those of other forms of acute bronchitis. Coryza is a much more frequent and dominant feature. The conjunctiva may be congested. The mucous membrane of the throat is deeply reddened and the tonsillar pillars present a heavy cyanotic color. Nasal discharge is frequently present; and associated laryngitis, in which the mucous membrane is markedly engorged, edematous, and cyanotic, is frequently met with. This may be accompanied by loss of voice. The skin of the face is usually congested, and on account of the associated cyanosis presents a peculiar bluish-red hue. There is commonly a facial expression of weakness and exhaustion out of proportion to the other physical signs. The temperature is usually higher than that seen in the other forms of bronchitis, frequently reaching 103° F. (39.44° C.) during the first two days of the illness; but it quickly drops to normal by the fourth or fifth day. The pulse rate is not increased in proportion to the temperature. It characteristically remains between 80 and 90 throughout the course of the illness. Respiration is decidedly increased and moist râles may be heard generally over the thorax. Frequently, however, the bases give the only physical evidence of exudation and occasionally one side only may be involved. The striking features, then, of this form of bronchitis are severe cough, with added symptoms of marked infection or intoxication, associated with pronounced evidences of coryza, and these all of a degree not seen in simple acute bronchitis.

Capillary Bronchitis

Definition.—Infection of the finer ramifications of the bronchial tree is usually associated with extension of that infection to the lung parenchyma, giving a bronchopneumonia. It is, therefore, difficult to present an exact clinical picture of this entity. Pathologically, however, it exists and occasionally one sees it when all the data massed fail to show pneumonic involvement.

Symptomatology.—It appears most frequently in the extremes of life, in infancy and old age. In the former it is often a primary infection beginning suddenly with a temperature rising rapidly to 102° F. (38.89° C.) or 104° F. (40° C.). Dyspnea is the most pronounced symptom and respirations commonly reach 60 to 70 a minute. The respiratory act is short, jerky, and quick, and expiration is prolonged and difficult. The accessory muscles are used. Cough of a short, hacking type is usually present and unproductive. Cyanosis appears early and may be striking. Exhaustion is an early feature and is frequently associated with a pulse rate of from 120 to 140. In serious cases as the disease progresses the infant may pass into a stupor or coma which gradually deepens until the end. In less severe cases the symptoms enumerated above may moderate soon, the breathing becomes easier, the pulse slower, cyanosis less, and the child may pass slowly to complete recovery.

In the aged this form of bronchitis is commonly due to an extension from the larger bronchi. But again, cyanosis, dyspnea, and exhaustion are the characteristic features of the illness. At the beginning there may be little fever and the pulse rate is not accelerated. But the exhaustion and depression continue, the nights are restless from coughing, and the appetite is lost. In this weakened state bronchopneumonia not infrequently supervenes. It usually develops gradually. Temperature of a moderate degree appears; the pulse rate increases and exhaustion becomes extreme.

Occasionally the disease occurs in strong adults. The author has seen such a case recently. A strong, healthy woman of forty-four, after a game of golf on an extremely hot day, took a cold shower and drove in the wind several miles to her home. That night she became very short of breath; respirations were 40; she had a short spasmodic cough, with blood-streaked sputum, and showed showers of fine subcrepitating râles over the entire lung bed. With this she had a plastic pleurisy of the left axilla, and marked plastic pericarditis. The temperature was 100° F. (37.78° C.), and the pulse rate varied from 90 to 100. Cyanosis was marked and the patient sat upright for relief in breathing. All the symptoms and physical findings disappeared within forty-eight hours and in five days the patient was again about.

Physical Signs.—The physical signs of this form of bronchitis differ but little from those of the disease of the larger bronchi; and this difference is due to obstruction of the entrance of air through the smaller bronchi into the alveoli. In children, the upper part of the chest is usually full, while the lower part is drawn in by inspiration, making the intercostal spaces prominent by their retraction. If the obstruction is extreme and over large areas, atelectasis therefrom may give temporary impairment of resonance which, however, disappears when the air again enters this part. On auscultation the respiratory murmur varies throughout the lung bed, depending upon this same obstruction. Over the area of lung which has little involvement the breath sounds are vicarious and harsh, and quiet or absent over the areas, particularly the bases, where collapse of the vesicles has occurred from obstruction.

Clinically, therefore, this form differs from a simple acute bronchitis in the frequency with which it attacks infants and the aged, its greater severity, and its tendency to develop into or to be associated with bronchopneumonia. Dyspnea, cyanosis, tachycardia, and decided weakness are also present in a degree seldom met with in the other forms of bronchitis.

Physical Findings.—The physical findings of acute bronchitis are few. Occasionally in the old, and in very young children, dyspnea may be associated with moderate cyanosis. Coryza may be present and the mucous membrane of the throat may be engorged and reddened. In the type which is superimposed upon tonsillitis, the tonsils are enlarged, and reddened, and the neck glands give evidence of infection. In children this avenue of invasion is apparently of more importance than in adults.

Inspection.—Inspection of the thorax offers little of note. If the bronchial secretion is marked, expansion may be limited with retraction of the lower part of the thorax. Occasionally the exudate may be so abundant in the larger bronchi that bronchi are palpable. These may be felt over the front of the thorax in the median area, or over the whole thoracic back.

Percussion.—The percussion note is usually little changed. Moderate dulness is occasionally percussed over the bases. At other times the thoracic note is hyperresonant.

Auscultation.—Auscultation gives us our most valuable physical findings. When the disease is limited to the trachea and larger bronchi a few large bubbling or sibilant râles may be audible. But if the smaller bronchi are the seat of the exudate, small, moist râles may be present. They are usually heard on both inspiration and expiration and are much more frequently found in the back than over the front. This is apparently due to the effect of gravity on the secretion.

It is important to recognize these various types of râles as they aid us to determine the size of the bronchi involved as the disease extends downward into the smaller tubes. It is also worthy of note that the râles of bronchitis are very fleeting and changeable things, disappearing in a few hours from an area in which they have been very abundant and appearing in a location in which previously no evidence of exudation has been elicited. Persistent râles over a localized area are usually indicative of lung involvement, and if these are small, crepitating, and soft in character and inspiratory only in time, they indicate that the alveoli contain a secretion.

Laboratory Findings.—An enormous amount of work has been done upon the sputum of bronchitis. The early workers hoped to find an organism to which they might ascribe its etiology. In 1892 Pfeiffer[6] published his work upon the influenza bacillus which he believed to be the cause of epidemic influenza, and after this it was thought by many that it might be the cause of catarrhal inflammation of the bronchial tree. In 1905 Lord[7] published the result of his work along this line. In the sputum of 59 per cent. of his patients with bronchitis he found an organism of the morphology and staining reaction of the Pfeiffer bacillus. However, it was not in pure culture but was commonly mixed with many other organisms such as the pneumococcus, streptococcus, staphylococcus, micrococcus catarrhalis, and occasionally Friedlander's bacillus. At that time he expressed the opinion that the influenza bacillus should be regarded as an important infecting agent in a large number of acute and chronic disturbances of the bronchi during the interepidemic period, and as a contributing factor in many other cases that showed mixed infection. This mixture of organisms in the sputum might well be expected when we recognize that the mouth, larynx, and trachea commonly harbor these bacteria and that the bronchial surfaces are exposed to the extension of such infection as well as to the inhalation of dust, which is always laden with microbes.

Although a few cases of acute bronchitis have been reported as due to pure cultures of the organisms commonly infecting the respiratory mucous membrane, the clinical picture of these cases differs in no way from that of those cases having mixed infections; and as the great majority of observers have found mixed infections of variable nature and combination, the consensus of opinion seems to be that as yet there is no known organism which is common to this disease. However, in the author's work, he attempted, with the coöperation of Dr. Wade Oliver, to classify his cases from the bacteriological view-point only to meet with the same experience as that of others, namely, that the organisms found one day, even in predominating numbers, might disappear completely in the second specimen of sputum examined when an entirely different group of organisms might be present. For instance, in one examination staphylococcus aureus with micrococcus catarrhalis was found, the former in large numbers; while a week later, in sputum collected, washed, and cultured with the same care a pneumococcus Type IV predominated with a short chained streptococcus. From such inconstant bacteriological findings we are forced to conclude that each individual case has special bacterial findings of its own and that there is no single organism which alone has the ability to produce catarrhal involvement; and that the bacteriology in the great majority of cases is a mixed one; and often this mixture, with the predominating types, changes frequently.

Microscopy.—The sputum contains little of microscopic interest. As a matter of fact its examination is important for its negative findings. In addition to the increased mucus seen in the first stage there are a few white blood-cells, and a few bronchial epithelial cells. Occasionally the latter are so numerous that a "desquamative bronchial catarrh" has been named therefrom. As the white cells infiltrate into the bronchial mucous membrane the sputum becomes yellowish or greenish in color.

Blood Findings.—The leukocytes in the blood are little affected in this condition. Forty-two per cent. of the author's patients had a white blood-cell count below 10,000; only occasionally did one rise above 15,000. Any increase above this count was usually associated with some complication such as tonsillitis, suppurative otitis media, or extension into the lung bed.

Diagnosis.—The diagnosis of acute tracheobronchitis is easy in the great majority of cases. With a history of cough following "catching cold," a tickling or raw feeling beneath the sternum, and a finding of râles scattered throughout both sides of the thorax there can be little reasonable doubt as to the nature of the illness. But there are, as in all other diseases, unusual cases which baffle the most experienced observers and which call for detailed study to eliminate all other possible conditions. In such cases Frankel[8] tersely says that the cause must be ascertained, and Hoffmann more elaborately tells us that when such cases are encountered one must not rest without inspecting the whole tract thoroughly, keeping in mind all possible conditions arising from the nose, larynx, and trachea; also the presence of a foreign body, tumors of the bronchi, and stenosis of the bronchi must be thought of and eliminated. He suggests that in these unusual cases it is necessary to examine the heart, great vessels, and the mediastinum, and to test repeatedly for tubercle bacilli before making a diagnosis of simple acute bronchitis. These suggestions and precautions are particularly pertinent in cases of recurring acute bronchitis and in cases which tend to develop into a chronic state.

As many cases of acute bronchitis appear early in the course of other specific diseases this possibility should be kept in mind. In children it may be the beginning of measles or whooping-cough. The former should not be difficult to differentiate with a history of exposure to infection and the presence of coryza with Koplik spots in the buccal mucous membrane. The latter is differentiated by the paroxysmal attack of severe cough associated with vomiting and the pathognomonic inspiratory whoop. At the beginning of these diseases it may be impossible to recognize the bronchial symptoms as due to them, but as time passes their characteristic symptoms and findings make diagnosis easy.

In adults acute bronchitis may appear early in the course of typhoid or pneumonia. Although it has not been common in the author's experience in the former, when it does occur the patients seem definitely more ill than they should be with simple bronchitis. And still the leukocyte count remains low. The cause of this condition is easily established by the finding of rose spots, positive blood culture, or isolating Eberth's organism from the stool or urine.

Tracheobronchial catarrh may be the initial finding of lobar pneumonia. Ordinarily, after a day or two have elapsed, the physical finding of dulness, increased fremitus, and bronchial breathing over a localized area makes the differential diagnosis easy to establish. In children and the aged bronchopneumonia frequently offers difficulty, for in this group it is often unrecognized if one depends upon the physical signs of infiltration and consolidation, which may be indefinite or even absent. Clinically, however, the patients with bronchopneumonia present a much more serious picture as they are markedly cyanotic, dyspneic, and definitely weakened. The x-ray is our most valuable adjunct in differentiating the obscure cases of this nature. It not only gives the typical shadow of bronchopneumonic consolidation but in addition localizes and defines the extent of this involvement.

Syphilis is another disease in which acute tracheobronchial symptoms are not infrequently seen. In the author's series of 249 cases of acute bronchitis, where the Wassermann test was made as a routine, 20 patients gave a positive reaction. These did not show unusual peribronchial adenopathy by physical findings or x-ray study, and were relieved by ordinary measures for the treatment of bronchitis. From the author's observation he does not feel that these cases differ in a clinical way from those of ordinary acute bronchitis, but possibly patients with syphilis may be less resistant to simple infection.

At times difficulty is encountered in differentiating acute bronchitis from early pulmonary tuberculosis. A history of exposure to tubercular infection with a finding of persistent râles, usually apical, and a radiographic finding of slight infiltration in the parenchyma of the lung give most valuable data in attempting this differentiation. If the patient has sputum, repeated attempts should be made to find the tubercle organism. Its absence, however, cannot eliminate the existence of early tuberculosis.

Complications.—Occasionally the coryza associated with acute bronchitis may be so severe that complications arise therefrom, such as conjunctivitis, or the infection may extend through the eustachian tube and give rise to acute catarrhal or suppurative otitis media. Six cases in the author's group had abscessed ears, and 2 were complicated with mastoiditis. Laryngitis may be present and give rise to the most severe symptoms of the illness. In the group of cases associated with an attack of acute tonsillitis, 4 of the author's patients developed acute polyarthritis. The same condition complicated 2 cases in which there was no clinical evidence of recent tonsillar or other focus of infection.

If the infection extends down the bronchial tree to the bronchioles, bronchopneumonia may supervene, and this is the most serious common complication of the disease. Seven patients in the author's series developed this.

Pleurisy is occasionally seen, and an active or slowly developing tuberculosis may be lighted up following a simple bronchial cold. Attacks of acute bronchitis tend to recur; a few cases develop into chronic bronchitis.

Clinical Varieties.—In the past many attempts have been made to classify cases of acute bronchitis. Marfan[9] suggested that each case be classified upon an etiological basis and he classed as specific types those from bacteria entering from without, as found in measles, influenza, whooping-cough, diphtheria, pneumonia, etc.; and those from bacteria entering from the blood, such as seen in meningitis, and occasionally in typhoid and secondary syphilis. In the nonspecific group he placed those cases arising from colds, nasal catarrhs, inhalation of dust, gases, etc. This classification is based upon the cause of each attack and is useful in the study of any case. But it fails to give us the anatomical aspect of the disease which is so necessary for the prognosis of each case. Often also it does not tell us of the type of organism causing the infection. Whether the disease is limited to the larger or to the smaller bronchi or to the bronchioles, and what the infecting agent is are most important data for clinical classification of each case. Ewart's[10] classification of acute bronchitis of the larger tubes and of the smaller tubes, and chronic bronchitis seems to cover the field from the anatomical point of view. If in addition each case can be studied bacteriologically we have the most complete data possible for the individual interpretation of each case. For instance, one may have acute bronchitis of the larger bronchi with a mixed infection, while another may have bronchitis extending to the smaller tubes due to the influenza bacillus.

Treatment.—Acute bronchitis, either in its simple form or associated with the conditions previously mentioned, is the most common disease both in civil and military life. The laity, however, regard it as of such slight significance that they seldom seek the advice of a doctor but employ home remedies, and often with apparently good result. This attitude is shared by many physicians who speak of it as a simple cold which the patient will soon throw off. Occasionally such casual methods are followed by severe complications or by fatal consequences, as illustrated by the U. S. Public Health Report which records about 12,000 deaths a year from this disease alone. This is a rather startling figure as it gives to this simple disease the rank of thirteenth in the mortality record of our country. This general indifference to cold, or bronchitis, is explained by the fact that the disease has a tendency to abate quickly and also that there is no specific therapy for it. From what has already been said one may readily see that there is no uniform treatment and that each case must be individualized in management. The old adage "treat the patient and not the disease" is well applied here. The object of treatment is first, to help clear up the infection in as short a time as possible, and second, to prevent infection from extending down the bronchial tree, and third, to protect those who may be in contact with the sufferer from getting the disease. By the time the physician is summoned after the failure of home remedies, the disease is apt to be well advanced and complications already in evidence. This robs him of a chance to attempt abortive treatment which, if inaugurated early, may shorten the illness by days and prevent serious sequellæ.

Abortive treatment is applied to strong individuals when seen in time while the infection is still in the upper respiratory tract or larger bronchi. It consists of **rest in bed, hot baths, saline cathartic,** and **quinin** and **urotropin** internally. Many cases cared for in this manner respond promptly. The continental idea of rest in bed for colds has not received the recognition it deserves in our country, for with this alone many patients show marked improvement and are spared a long illness. The room should be sunny and have frequent changes of fresh air. The temperature must be graded according to the need of the individual. The young are ordinarily relieved by cold air while the old and infants may suffer from paroxysmal coughing in too low a temperature. Occasionally night air produces these symptoms and **steam** or **medicated vapor** added to the air of the room at night may be soothing and alleviate spasmodic nocturnal coughing.

Hot baths of a temperature of 100° to 105° F. (37.78° to 40.56° C.) for ten minutes are usually followed by free perspiration which is increased by giving **hot drinks,** such as **lemonade.** The common practice is to advise these baths at night after which the patient gets into a warmed bed and keeps well covered. The following morning an ounce of **Epsom salts** is given and the patient is kept on a **liquid diet,** forcing water throughout the day. Quinin and urotropin in 7 grain (.46 gram) doses are given every six hours; apparently the former acts as a diaphoretic, and both apparently have some bactericidal action upon the organisms of the bronchial mucous membrane.

If the abortive treatment fails one has left a choice of **local applications, inhalations,** and **internal medication.** Although the laity uses all sorts of material for poulticing, **flaxseed** and **mustard** are those most commonly recommended. They should be applied while very hot after the skin has been thoroughly covered with vaseline. It is the author's practice in using poultices in acute bronchitis to apply them to the entire front as well as the back of the thorax. The poultice should be covered with paper or rubber sheeting so as to retain the heat, and it should be changed as often as necessary to hold the heat and to give comfort to the patient. This treatment is usually followed by less cough, and the substernal pain is materially relieved. The value of this treatment is questionable as regards the course of the illness or the physiological effect it has upon the disease process, but, clinically, it not uncommonly changes the condition of a distressed individual to one of comparative ease. On the other hand certain persons get greater relief from **cold compresses** which should be iced before being applied and then covered in with a bath towel to prevent wetting the clothing and bedding. Cold seems more serviceable when there is marked dyspnea and cyanosis, for it is associated with an increased depth of breathing which is accompanied by better aëration of the blood.

In those acute cases in which cough is of a dry, spasmodic, exhausting character inhalations may be of service. Steam or some medicated vapor commonly relieves the bronchial irritation by their soothing properties. **Compound tincture of benzoin,** a dram (4 grams) to a quart of boiling water, is as good as any medication for this purpose. At times **eucalyptus** or **menthol** are substituted. If there is no steaming apparatus available, the water can be kept boiling by a gas or electric heating appliance and the volume of steam may be increased by stirring. It may be kept close about the patient by a canopy improvised of heavy paper or a bath towel. Inhalations may be repeated every four hours if they prove of value. It is necessary after this procedure to protect the patient from draughts or exposure.

In the past there have been many advocates of direct medication for acute infections of the upper respiratory tract and bronchi and aromatic oils are used for this. Recently Voorhees[11] has recalled our attention to this method of care. He has used **oil of cloves, cinnamon,** eucalyptus and menthol directly applied to the mucous membrane involved. They are given after the larynx is sprayed with a 2 per cent. solution of **cocain.** The oil is given in 10 per cent. strength in **liquid petrolatum** as its vehicle. As a result of his study he feels that menthol is the oil of preference and he uses it in from 5 to 25 per cent. strength. In acute bronchitis treatment was given at intervals of from eight to twelve hours, and among his cases marked improvement took place within seventy-two hours, unless the bronchitis was of pneumococcus or streptococcus origin. He feels that the oil vehicle not only covers the irritated mucous membrane, but the analgesic action of the volatile oil relieves the cough as well as stimulates expectoration and possibly has some bactericidal action.

The use of internal medication calls for careful discrimination. At the beginning of the illness the object of this would be to diminish bacterial infection. Considerable work has been done with the idea of obtaining positive data which might thus help in treatment. It is known that quinin inhibits bacterial growth in the air sacs of the lungs, and possibly for this reason it has been given for infections of the upper respiratory mucous membrane. Of late urotropin has been considered to have bactericidal properties on organisms of the respiratory tract. Armstrong and Goodman[12] first detected **hexamethylenamin** in the sputum after daily doses of 25 grains (1.62 grams), and Heitmuller[13] and Miller[14] both advocate its use in common colds and bronchitis. Since their work many have used the drug with varying results. Vanderhoof[15], from his observation, believes that it is of great value in coryza in which not only the stage of catarrhal inflammation is shortened but the succeeding bronchitis may be modified or prevented. Recently Neves[16] studied the effect of urotropin in 92 cases of bronchitis in children, 18 of which were acute; 5 only were helped. He tested the split products of the drug in the sputum and urine and found that it was eliminated in two hours by the kidney, while little was found in the sputum. He concluded that it was not a sure therapeutic adjunct in the treatment of bronchitis, although it had been given in rather large doses,—15 grains (.972 gram) were administered in infants up to two years of age; 30 grains (1.95 grams) from two to five years; and 45 grains (2.926 grams) from five to ten years.

Iodin is another drug which has enjoyed the reputation of having germicidal action upon respiratory infections. Apparently this is based upon clinical observation or is deduced from its action of increasing and facilitating the secretion of the bronchial mucous membrane. The author can find no substantiated proof of its specific germicidal action by experimentation. Recently Blum [17] expressed his views in an article entitled "Iodin as a Specific Germicide in Respiratory Infections." But he failed to show it had such action in his report.

Since the work of Seibert [18], who demonstrated the bactericidal action of **camphor** on the pneumococcus in the degree of concentration in which the drug was eliminated from the respiratory tract, many have become advocates of its use in upper respiratory infections. It can be given as **camphoric acid** or **sodium camphorate.**

Beside using medication with the idea of preventing extension of the infection many symptoms call for specific treatment. If the cough is irritating in the early stage, **Dover's powders,** grains 10 (.65 gram), every six hours, may be serviceable. Many use this at the beginning of the illness on account of its diaphoretic action. In the majority of cases the cough is followed in a short time by expectoration which is raised without much difficulty. This is a useful act and should not be suppressed. If the secretion is so tenacious that coughing depletes and exhausts the patient, the ideal treatment would be to diminish the cough to a point of comfort and increase the expectoration. This cannot always be brought about and it is particularly hazardous to try with infants, young children and the very old, for it may be associated with a retention of mucus to such a point that the patient may veritably suffocate. On occasions both objects may be tried for and in the author's hands **heroin,** which depresses the cough, combined with a stimulating expectorant, such as **terpin hydrate** is often of value. Another stimulating expectorant of proved worth is the following:

℞
Ammonii Chloridum........................ʒ 2 (7.80 grams)
Ammonii Carbonatis........................ʒ 1 (3.90 grams)
Mistura Glycyrrhiza Composita ad.........℥ 4 (124.40 grams)
Sig.—Teaspoonful every 4 hours.

At times **codein** may be useful in controlling an exhausting cough, or even **morphin** may have to be resorted to. Occasionally small doses of the latter give temporary relief and it appears to be indicated particularly in cases where dyspnea is a marked feature. But, again, we must not forget that this symptom is met with most often when the smaller bronchi are involved and that cough is necessary to keep the secretion from blocking these bronchi. In children emetics have a place when mucus accumulates to a point of threatened suffocation. **Syrup of ipecac** may be used with good result. **Apomorphin,** hypodermically, grain 1/30 (.00216 gram), has been advocated, **strychnin** being combined with it to control its depressant effect. Jacobi once recommended the spanking of an infant, if dyspnea and cyanosis were marked, for he felt that the deep breathing occasioned by this would produce the same effect as an emetic.

In addition to the treatment of symptoms of this affection general care is necessary to shorten its course and to support those who are seriously ill. This especially applies to the treatment of the aged. **Water** should be given freely, at least a glass every two hours, for it aids in eliminating toxic substances which might in turn continue the irritation of the bronchial mucous membrane. At times liquid foods may be substituted for the water, such as **milk, malted milk, chocolate, tea, coffee, broths,** which, in addition to the fluid, carry a certain degree of nourishment. They do not tax the digestion and are not liable to be associated with gaseous distension of the stomach and bowels. In the ordinary case soft foods should be used to keep up the patient's strength, but with the aged, who commonly have no appetite, liquid food given at stated times should be considered part of the medical treatment.

Sometimes patients are unable to sleep at night. Rest is necessary to conserve strength and should be obtained whenever possible by the use of some simple soporific, 20 grains (1.3 grams) of **ammonium bromid,** or 10 grains (.65 gram) of **medinol** usually give relief. If sleep is disturbed by nocturnal coughing, codein or even morphin in small doses may be resorted to, if there are no contrary indications. In the aged other general supportive measures are occasionally demanded. Strychnin can be used as a tonic as well as a respiratory stimulant. If necessary **caffein sodium benzoate,** 5 grains (.324 gram) every four hours, or some **digitalis** preparation may be used to support the circulation. Daily care of the bowels is obviously indicated and this may be done with a simple enema or mild cathartic. In the young and strong a saline may be beneficial even after the primary catharsis at the beginning of the illness. In the weakened, drastic catharsis should not be continued.

Preventive Treatment.—In the past little attention has been paid to this very common and simple malady. The war, however, has taught us its seriousness from the degree in which it impaired the efficiency of the army. Vaughan and Palmer in their study of communicable diseases estimated that 80 per cent. of all the troops were infected with bronchitis at Camp Oglethorpe. Many cases were serious enough for hospital care, and many patients who were not so treated yet had their efficiency reduced by their condition. Soper believed it to be the most significant disease of the war, not even excluding influenza. He made this statement, first, on account of the time lost by the countless number of men affected; second, because of its connection with other respiratory diseases; and third, because it provided the means for the spread of infections which, though not strictly respiratory, are believed to be transmitted in the respiratory manner. He believed that the prevalence of acute bronchitis was due to an indifference as to its importance, that it was not dealt with as a contagion, and that hygienic measures to prevent the disease were not logically carried out. His recommendations were that early cases should be detected and properly isolated, infected material from them should be disposed of properly, and that promiscuous coughing, sneezing, and spitting should be prohibited. Emerson estimated that the patients suffering with acute bronchitis each lost six and three-tenths days from service and that the decrease of efficiency was such that preventive methods should have been diligently carried out. It was his opinion that other factors than those already mentioned, such as overcrowding, inadequate ventilation, exhausting drill, and heavy exposure were etiological factors in no small number of cases.

Zinsser felt from his study that the natural resistance to bronchitis and pneumonia is very high in all human beings if their tone is kept up, but when this is diminished by fatigue, insufficient food, and heavy exposure individuals are attacked and epidemics follow. Delavan[19] and Minchew[20] each worked with infections of the upper respiratory tract as they occurred in epidemic forms in camps. From their studies they formulated the working rule that all infections of the upper respiratory tract should be treated in quarters and that contacts should be treated to prevent epidemic spreads. **Dichloramin-T** in 2 per cent. solutions was used as a spray and the results in abating the epidemic were gratifying. They felt that many cases of acute bronchitis were and could be prevented by active treatment of infections occurring in the upper part of this tract. It seems also that in civil life spraying the nose and throat with dichloramin-T or 15 per cent. **argyrol solution** at the beginning of simple colds is a procedure which offers some effect in the prevention of the extension of the infection to the bronchial mucous membrane. If in addition patients can be moderately isolated and kept at a safe distance from those with whom they must come into more or less contact, and can be taught not to cough or sneeze promiscuously, much can be accomplished to prevent the spread of this infection to others.

Pathology.—The pathology of acute bronchitis is very meager as most patients recover. The cases studied postmortem are those which terminated from some disease in which bronchitis was only a part, such as pneumonia or bronchopneumonia. The mucous membrane of the bronchi is reddened and swollen. Occasionally hyperemia is so severe that small hemorrhages exist. In this stage secretion may be lacking or limited to a small amount of tough mucus. Sometimes the membrane secretes a serous exudate which contains a few blood corpuscles. After a period of a few days the white blood-cells which have infiltrated the mucous membrane reach the exudate and give it its purulent character. In the smaller bronchi the above changes lead to narrowing of the lumen so that the entrance of air is difficult; in severe cases it may be impossible. This is observed in capillary bronchitis. It gives rise to atelectasis and favors the development of bronchopneumonia. As the result of this mucous membrane change, the epithelium becomes loosened and may be pushed off in the bronchial secretion, uncovering the congested blood-vessels beneath. The glands of the bronchial wall increase in activity and secrete a mucus or mucoid pus. In cases where the inflammation lasts a long time, or frequently recurs, the submucous layer is infiltrated and hardened or even partially destroyed. The peribronchial glands are usually enlarged but there is no tendency to pus formation. Apparently these changes are not marked in the ordinary case of bronchitis and repair is accomplished quickly with little residuum caused by the changes.

History.—Badham's[21] interesting little monograph gives us what is known of the very early observations of bronchial conditions. He is credited with the introduction of the term bronchitis, and before his time it was usually confused with other diseases of the respiratory system, such as tuberculosis and pneumonia. He tells us that "some nice distinctions with regard to the specific diseases of the organs of respiration seem to have prevailed from a very early period in the history of medicine; pleurisy, for instance, pneumonia, pleuripneumony can hardly be better described at this day (1808) than they were by Areteus." Areteus also recognized and discussed the treatment of asthma, and then entered into an argument about an affection which appears to be bronchial. The symptoms he gives appear to indicate a bronchial inflammation, but under what precise conditions they arise or what changes they undergo cannot be readily determined. Aetius had apparently the same disease in mind when he wrote "Concerning That Affection Which Is Thought to Be Pleuritic but Is Not." In this he says, "In this disease it is not from pain the respiration is impeded but simply from obstruction of the air tubes." Thus it will be seen that the physicians who flourished in the early days of the Roman Empire were awake to the necessity of recognizing both true parenchymal pulmonary disease and also diseased states of the bronchial tubes.

Sydenham gave an account of the symptoms, causes and manifestations of an affection decidedly inflammatory in character having its seat in the bronchial mucous membrane, and he states that such a condition had long been known and often casually described but that it had been regarded as of little significance and had been imperfectly understood. Hence credit has been given to Sydenham for the first accurate account and the first most nearly complete presentation and understanding of the inflammations of the bronchial mucous membrane.

In modern times an impulse was given to the general interest in the disease by the work of Laennec. He probably contributed more than any one else to the proper anatomical and clinical understanding of the condition. With the use of percussion and auscultation he studied the physical findings accurately and made careful differential diagnoses of the various types. After his invention and perfection of the stethoscope he coined many descriptive words which have become the accepted and classic terms in speaking of the physical signs of bronchitis.

With the development of the microscope, pathologists arrived at a further knowledge of the tissue changes in the bronchial wall and the disease came to be studied with more detail and insight. In the monographs of Hoffmann and Fraenkel one finds in a most satisfactory degree a correlation of the clinical and pathological findings. In fact so thorough is the work of these authors that it would be difficult to add anything to it until the time comes when we may arrive at a better understanding of the responsible underlying pathogenic organisms.

CHRONIC BRONCHITIS

Etiology.—Chronic bronchitis is a term usually applied to a group of symptoms, cough, expectoration and dyspnea, after they have existed for a period of time or recur in repeated attacks. This symptomatic recognition of a disease entity is doubtless due to the numerous cases in which it is secondary to other diseases. There are, however, primary cases of simple chronic bronchitis which arise from chronic catarrhal inflammation of the bronchial mucous membrane following repeated attacks of acute infection, or which insidiously develop where one cannot find the factors which place them in the secondary group. Again, in those cases which are secondary or dependent upon other diseases, chronic bronchitis may become so important that the original cause sinks into the background. Hoffmann[22], from the study of the causes of his cases of chronic bronchitis, uses the following grouping:

1. The form of simple bronchitis following acute bronchitis, measles, whooping-cough, repeated colds, and influenza, which he believes should be classified as chronic when the duration of symptoms exceeds forty days.
2. Chronic bronchitis occurring in constitutional diseases such as rickets, scrofula, Bright's disease and so on.
3. That group due to mechanical injuries such as smoking, inhalation of dust and heavy drinking. In this he includes those cases found among glass workers, bakers, millers, and tobacco workers.
4. In group four he places those cases arising from the diseases of the nasopharynx, including rhinitis, chronic tonsillitis and sinusitis.
5. In the fifth group he places those forms depending upon circulatory changes, such as heart disease, including mitral insufficiency and stenosis, aneurysm, arteriosclerosis, and myocardial insufficiency from any cause.
6. This group includes those forms of chronic bronchitis which occur in all chronic lung diseases, such as tuberculosis, bronchiectasis, emphysema, lung tumor, and pleural disease.

Fraenkel[23] also accepted this classification and the cases studied by him fall naturally into this division.

Lord[24], from his study of 161 cases with symptoms of chronic bronchitis coming to autopsy at the Massachusetts General Hospital, found that the majority fell into three groups:

First, 63 per cent. were associated with passive congestion of the pulmonary circulation in consequence of cardiac insufficiency. The cause of this insufficiency varied, covering broken compensation due to valvular and myocardial disease, chronic adhesive pericarditis, diseases of the coronary vessels, arteriosclerosis, chronic nephritis, syphilitic aortitis, and aortic aneurysm.

Second, he placed in a group those cases of chronic bronchitis arising in the course of pulmonary disease. Nineteen per cent. of this group, or 31 cases, were found to be associated with tuberculosis; 22 cases of the chronic ulcerative type, and 9 of the miliary form. He believed that the bronchitis was due to secondary invaders and its frequency was explained by these invaders developing on account of the lowered resistance of the patient or of abnormal local mucous membrane conditions. Other pulmonary conditions in which chronic bronchitis was present in his series were subacute or chronic bronchopneumonia, lung abscess, bronchiectasis, malignant disease of the lung, and pulmonary embolism and thrombosis. He also mentions echinococcus disease, actinomycosis and pneumonokoniosis as occasional, primary conditions upon which chronic bronchitis supervenes. He further speaks of the fact that chronic infections of the upper part of the respiratory tract such as rhinitis, pharyngitis, and tonsillitis may be the starting point of this illness.

Third, he places in a group those cases arising from bronchial disease. He has found that 3.7 per cent. have suffered from bronchial asthma. Bronchial stenosis from any cause, such as syphilis or tumor pressure, was occasionally found as a basis of the chronic bronchitis.

In 120 of the author's own cases, in which chronic bronchitis dominated the clinical picture, he found that 87 were secondary to some of the etiologies above mentioned, and that 34 were of the primary simple chronic form. Of the secondary cases, 41 were associated with myocardial insufficiency. This insufficiency was dependent upon valvular disease, arteriosclerosis, hypertension, and chronic myocarditis. Six cases were associated with pulmonary disease; 5 with tuberculosis; 1 with anthracosis; 10 were associated with asthmatic attacks or occasioned by them. Three cases were associated with syphilis, although careful examination failed to find tracheobronchial syphilis. The remaining cases fell into the constitutional or infectious group, such as rickets, gout, scarlet fever, septic infection and influenza.

Hence it will be seen that most cases of chronic bronchitis are symptomatic of or secondary to other primary diseases. It is therefore obvious that its clinical picture and course must vary widely in these different groups. It is not the purpose of this article to enter into clinical discussion of the primary diseases with which it is associated, but we plan to present first simple chronic bronchitis, and then to discuss briefly some of the clinical aspects of the groups mentioned when they are prominent enough to give the associated bronchitis some unusual features.

Symptomatology.—COUGH.—Of the 34 cases of the author's series classified as primary simple chronic bronchitis, cough stood out as the one important symptom. It was present in all cases. Its duration varied: in 9 cases it had existed from two to twenty-two years; and in 9 cases it had run from two months to six months. Many of these patients had had recurring attacks of such frequency that they were classified in the chronic group. Apparently there was some inflammation of the mucous membrane persisting between the attacks which made them susceptible to recurring infection. Again, their occupations predisposed them to recurring attacks, for by far the greatest percentage were seafaring men or men working along the docks of whom was demanded heavy work and who were unduly subjected to exposure. Excessive use of alcohol and improper hygienic conditions of living were common factors in causing these recurrences. Many of the patients complained of cough only during the winter months, remaining entirely free from it during the summer. This winter cough is characteristic of this form. Patients state that they have colds once or twice in the fall and then the cough continues throughout the cold weather. It varies greatly in character. At times it is quite insignificant; at other times, severe, irritating, and painful. It is usually more severe in the morning, at which time the patient raises a moderate amount of sputum. During the day it may be quite absent, only to appear again at night when the patient lies down to sleep. As warm weather comes on it moderates and even may disappear so completely that the patient does not suffer again the following winter. There is, however, a tendency to recurrence, and in the more severe cases it returns in an aggravated form each year. Finally the cough becomes more troublesome; sleep may be much disturbed by it and dyspnea appears and progresses.

In the early part of the disease patients carry on their vocations, retain their bodily vigor, and look apparently well. After many recurrences, acute exacerbations of infection are prone to occur which necessitate confinement. The patients may then lose weight, become emaciated, and present the picture traceable to this chronic infection and its distressing symptoms.

EXPECTORATION.—This varies as much as the cough. In the beginning the latter is usually dry and unproductive while at a later time, or with recurring attacks, mucus and, later, mucopurulent sputum may be raised. Sometimes this is blood-streaked or hemorrhagic. If the disease continues for a long time, the sputum becomes mucopurulent in all cases.

SHORTNESS OF BREATH.—This was a symptom complained of in 6 of the author's 34 patients and was always associated with an increase in the lung volume. At the beginning of the illness dyspnea is not present but as emphysema develops it appears and increases and in the later stages may be the most pronounced symptom. At times it is paroxysmal and resembles that seen in asthma. In the progressing cases emphysema and dyspnea are associated with cyanosis which may become extreme. Later if cardiac failure supervenes there may be enlargement of the liver and clubbing fingers. In certain cases of a progressive type the terminal picture is of cardiac failure, in which there is general body edema, with marked stasis in the pulmonary circulation.

CHEST PAIN.—This was complained of six times in this series. It was always caused by cough. It was described as a raw sticking pain beneath the sternum, or as a sore aching pain along either lateral thorax, passing to the epigastrium. Apparently the latter was due to strain, by the act of coughing, upon the attachment of the diaphragm or abdominal muscles to the lower portion of the thoracic wall.

Occasionally other symptoms were complained of in the author's group. Two lost weight; 1 had chills and fever; 3 showed edema; 2, extreme loss of appetite; 2 had palpitation; 4, general weakness. These were present in those cases that had progressed unfavorably for several years or were associated with complications. Fever was not present in the author's cases except at times of severe acute exacerbations or in complicated cases.

Course.—This simple chronic form is most often seen in civil life in persons past middle age who have had mild recurring attacks and have indulged too heavily in alcohol, tobacco, and food. Drawing his cases from the water front, the author had only 10 above forty years of age; 6 were from thirty to forty; and 18 were from twenty to thirty. Only 1 female was included in his group.

The course of simple chronic bronchitis is of itself not dangerous or painful when it occurs in persons before middle life, except for its tendency to recur. The general health of the patient may not be undermined for years so long as complications do not intervene. But in old people it takes a more unfavorable course, for the symptoms are usually more severe and there is a greater tendency to complications, and with increasing emphysema the dyspnea and all symptoms tend to progress and undermine the general health of the individual.

Physical Signs.—As this disease in its milder form affects principally the trachea or larger bronchi there are few physical signs in the beginning. It is to be remembered that the finding of râles is not necessary before one can venture on the opinion of chronic bronchitis. Commonly then, in the earlier part of the illness the lung examination is important principally for its negative value. If the disease continues, emphysema slowly appears and all obstinate cases finally give signs of pulmonary distension. In a few instances this progresses to such a degree that the elasticity of the lung is completely destroyed and the thorax takes on the barrel shape of advanced emphysema. Apparently the distension of the lung develops more rapidly in those cases in which the chronic inflammation passes from the larger into the smaller bronchi.

When emphysema first appears in the course of chronic bronchitis it gives also few or imperfect physical signs. The first one of importance is the full, loud hyperresonant note heard through the entire thorax. As the pulmonary distention increases the lung borders are extended; later, the cardiac area of dulness may be obliterated, and finally kinds of air-cushion pads or swellings appear in the supraclavicular fossæ. With these advanced findings of emphysema, the thorax is markedly increased anteroposteriorly; it moves as a whole and there is little outward movement of the ribs during respiration. Most cases, particularly during the times of recurring attacks, have sibilant squeaks and pipes continuously over both lungs. At such times moist, bubbling râles are likewise frequently present over the bases. There are cases also in which rhonchi are perceptible over long periods of time. At the beginning the breath sounds are vesicular, and if the exudate is marked they may be quite completely obscured. As emphysema appears they become distant, and at length expiration becomes prolonged.

Laboratory Findings.—The laboratory findings of the author's cases of chronic bronchitis were similar in all respects to those found in acute bronchitis. In the earlier course the blood did not show anemia, and the white cells and differential count were quite normal. At times of acute exacerbation of the chronic state a mild leukocytosis, reaching from 10,000 to 13,000, was present. With this a polynucleosis of from 75 to 83 per cent. was found. The sputum showed the same type of mixed infection as that which we frequently observed in the acute forms, and the same tendency to change of organisms, at various stages of the illness, was noted. Occasionally in the later states when insufficient circulatory symptoms appeared, the urine showed an oliguria, albumin, and casts.

Diagnosis.—The diagnosis of simple chronic bronchitis should be made by elimination. Only in this way can we be reasonably certain that those diseases, with which secondary bronchitis is so commonly associated, have been thought of and ruled out. We have therefore to think of and eliminate diseases of the heart and vascular system, such as valvular disease, arteriosclerosis, hypertension, syphilitic aortitis, and aneurysm; secondly, diseases of the respiratory tract, pulmonary tuberculosis, lung tumor, lung abscess, and pneumonokoniosis. Also to be ruled out are those diseases of the bronchi which cause symptoms which so often lead to a diagnosis of bronchitis as a primary affection, such as tracheobronchial syphilis, foreign body, bronchiectasis, and asthma. In this group Jackson[25] has repeatedly called attention to the usefulness of bronchoscope in all doubtful or atypical cases, and Bowen[26] believes that many cases of foreign body are incorrectly diagnosed as chronic bronchitis. He feels that a roentgen ray study of such cases often clears up this error, and, in addition, gives valuable differential data which are necessary to clarify certain types of chronic lung disturbances which are often labeled chronic bronchitis.

Recently 2 cases illustrating this point were admitted to the author's service with a diagnosis of severe chronic bronchitis. On bronchoscopic examination one showed a diaphragm-like stricture of syphilitic origin at the lower end of the trachea; the other, a piece of cancellous bone at the lower end of the left primary bronchus.

Of all the diseases that are to be eliminated from consideration before one expresses the opinion of chronic bronchitis, tuberculosis stands out as of first importance, as it so often begins with symptoms of mild bronchitis. Not only are careful and repeated sputum examinations indicated but repeated physical examinations should be made searching for evidence of localized increase in pulmonary tissue and localized areas of râles. In the great majority of cases these will be found at the apices. In suspected tuberculous cases too much importance cannot be attached to the family history. Pleurisy, hemoptysis, night sweats, fever, loss of weight and strength may appear in the past personal history. Fortunately the stereoscopic raying of the thorax aids materially in clearing up doubtful cases.

Special and Associated Clinical Types.—BRONCHITIS AND HEART DISEASE.—Although there has been an attempt in the past to describe clinically varying types of bronchitis in various valvular and myocardial affections of the heart they differ only in such small details that they will be considered here as of one group. It has been said that in mitral disease bronchitis is due to venous stasis, while that associated with aortic insufficiency is due to active arterial hyperemia.

Bronchitis in heart disease is most often found in mitral disease and most frequently encountered associated with mitral insufficiency. It is due to passive congestion of the lungs and begins with a finding of small moist râles over both bases. Here the breath sounds are diminished and the percussion note may be dulled. There is dyspnea and cough on slight exertion. If this congestion remains mild the cough is short and dry in type and has been described as "heart cough." If the congestion progresses, sputum appears; at first of mucoid character, it later becomes mucopurulent; occasionally it is blood-streaked. If the cardiac insufficiency becomes disabling, cough and dyspnea increase, and sometimes pulmonary apoplexy occurs. As a terminal stage pulmonary edema appears as an expression of complete circulatory failure.

In the bronchitis of mitral stenosis there may be attacks of dyspnea and cough accompanied by the raising of frothy mucus; this is often blood-tinged. On account of the tendency to hemorrhagic sputum in this group of bronchitis a diagnosis of tuberculosis is often made. Careful and repeated examinations should prevent this error.

BRONCHITIS AND RENAL DISEASE.—Again, several forms of chronic bronchitis have been described as having some unusual clinical aspects when they occur in certain forms of kidney disease. At the base, however, they are probably most often associated with cardiac insufficiency, although possibly some cases are of toxic or of nitrogen retention origin. If due to the former, the dyspnea is paroxysmal and nocturnal and expiration may be difficult and prolonged. This group of symptoms has given rise to the term "renal asthma." Here one usually finds sibilant as well as small moist râles throughout the entire lung bed. The râles are characteristically transitory and changeable in their location. A case of nitrogen retention origin was recently observed. A woman fifty years of age, with a blood-pressure of 250 systolic, 140 diastolic, appeared complaining of the above symptoms. Clinically she presented the classical picture of asthmatic bronchitis. Examination convinced one that it was associated with chronic glomerular nephritis. She carried a heart rate of 90 and showed no gross evidence of myocardial insufficiency. There was a blood urea of 140 milligrams per 100 c.c. and a uric acid of 7.5 milligrams. Treatment by depletion and elimination diminished these bodies 50 per cent. and with this improvement of her nitrogen intoxication all symptoms of bronchitis disappeared.

WAR BRONCHITIS.—We have previously discussed the prevalence of acute bronchitis during the war and emphasized the factors which caused this frequency as well as those conditions which favored recurrences. Chronic bronchitis was also very prevalent and Mantoux[37] describes interestingly this simple chronic type found among the soldiers. He believes that exposure to the hardships of the trenches and dampness are the factors which gave many their initial cough. Under these conditions the "cold" did not stop; the general condition of the patient was good, his temperature was normal, but his cough lasted for a few months until he finally entered the hospital. Cough and expectoration were the two symptoms most often complained of.

The physical signs in this type of bronchitis he found to be constant. They were dry sibilant râles and often rhonchi extending throughout the thorax. Occasionally they disappeared for a few hours or a few days only to reappear, and frequently they were of such intensity as to hide the normal respiratory murmur. If the men continued among the same surroundings these physical signs remained for months and gave the impression that the chest was filled or clogged with mucus. If treated under these conditions little benefit was found, while change of service yielded the best result of any management attempted.

SPECIAL FORMS.—In the past special forms have been named drawing their characteristics from the sputum. These are the dry bronchitis, or *catarrhe sec*, of Laennec; the serous form called bronchorrhea, or *catarrhe pituiteux* of Laennec; and a third form, a purulent bronchorrhea, or purulent bronchitis.

Dry Bronchitis of Laennec.—Laennec felt that the dry catarrh was present especially in persons with a gouty diathesis, but it appears very often in various stages of ordinary chronic bronchitis. The sputum is scanty and has some transparent pearl-like bodies, called *crachats perlés.* Occasionally it contains Charcot Leyden crystals and Curschmann's spirals. Among the distinctive clinical features is distressing paroxysmal cough, which is troublesome and difficult on account of the scanty secretion. This occasions pain over the lower thorax and a feeling of oppression in breathing. As the case continues emphysema appears and invariably complicates well-developed cases. Leannec believed that this form was due to swollen mucous membrane, most marked in the smaller branches, and later Cantani (Hoffmann) found a mucous membrane so swollen that diffuse bronchostenosis resulted therefrom. On physical examination one hears sibilant and small moist râles in moderate numbers. If there is a tendency to bronchial stenosis the respiratory murmur may be diminished or absent over that portion of the lung supplied by the bronchus which suffers most engorgement at any one time.

Serous Bronchitis of Laennec.—In this variety paroxysms of cough and dyspnea are relieved by expectoration of a colorless, watery, frothy material likened to gum solutions. At times the sputum is ropy like raw white of egg. The expectoration may reach large amounts, as much as several ounces at any one paroxysm. The cough is severe and irritating, giving decided dyspnea and hence the name asthma humidum has been applied. The paroxysms of cough, expectoration and dyspnea may appear at intervals through the day, most usually in the morning and evening. After the bronchi are relieved of this secretion patients are comfortable until the next paroxysm. The condition may last for years. Lebert (Hoffmann) mentions the case of a man who had such a bronchorrhea. He lived to be 82, although his health was poor and he had a tendency to evening temperature and dependent edema. As the disease progresses frequently lung and heart changes become associated with emaciation, anemia, and generalised edema.

Purulent Bronchitis.—Purulent bronchitis is the end form of most cases of advanced chronic bronchitis and the sputum then resembles that seen in chronic ulcerative tuberculosis. At times there may be large quantities of sputum daily; 500 c.c. or more are not uncommon. Its character is of the nature of pure pus. This condition is called purulent bronchorrhea. Various authors have described this as an independent condition although it may occur during the course of any case of chronic bronchitis and there are no strict differential data separating this group from the insidious primary group. Fever is usually present in this form. The disease may slowly undermine the patient to such an extent that terminal bronchopneumonia complicates. Many of the patients, however, in spite of the large amounts of purulent material raised, seem resistant to the illness and carry on their vocations indefinitely.

Treatment.—From the foregoing discussion of the various causes of chronic bronchitis it is apparent that the treatment in any one case must be individual. In the simple chronic form treatment should be directed not only to the relief of symptoms but to the prevention of recurring attacks. In the secondary form, in addition to these aims, the cause of the bronchitis should receive most careful consideration. In the former, intelligent direction of life may help to avoid recurring attacks. Patients should be instructed not to subject themselves to severe exposure of weather or temperature. At times a **change of occupation** is necessary to protect the patient from further progress of the disease. Those working in dust-producing occupations or cold storage plants or along the waterfront or as sailors may get complete relief by change of occupation to one where working conditions are more favorable or where they can have more suitable air. Frequently such a change is all that is necessary in treatment. But often patients have not the energy or means to accept such changes. Then they must be instructed to wear woolen undergarments winter and summer and to protect their bodies from sudden chilling at all times. Usually constitutional resistance may be increased by **cold baths,** either by sponging or by shower each morning. The general strength must be kept at a maximum by good food and long hours of sleep.

The use of **vaccines** in this type has many advocates. Eyre and Lowe[28] have made a favorable report, and Babcock[29], in a limited number of cases, used autogenous vaccines with gratifying success. He recognizes that the bacteriology of the bronchial secretion changes frequently and hence suggests that repeated examinations be made so that the vaccine is sure to contain the infecting organism at any one time. Robinson and Queen[30] studied 30 cases with much detail and report 22 cured after a year; 8 were not improved.

In the author's own experience certain of these cases responded very creditably to autogenous vaccines and it is an adjunct in treatment which is worthy of trial.

If in spite of the care given as outlined the patients continue with symptoms, a **change of climate** is indicated. This is also applicable particularly to that group of middle-aged and elderly patients who have the recurring winter cough. Many patients obtain complete relief of symptoms when in Southern California or Florida. Others get most benefit from sea air such as that of Bermuda or Jamaica. If these patients can lead an out-of-door life during the summer, the Adirondack and White Mountains and parts of Maine have climates which are bracing and beneficial. If symptoms persist in spite of this change, or patients are unable to leave home, no effort should be spared to obtain relief by internal medication, inhalations, and local treatment. The details of such treatment have been outlined under acute bronchitis. It must be remembered, however, that the therapy of chronic bronchitis gives much less certain results than that of acute bronchitis, and one must try this remedy and that measure until he finds the one best adapted to each individual.

When chronic bronchitis appears secondary to circulatory failure treatment should be directed to the cause of that failure and an attempt made to restore compensation. If a valvular lesion is at the base of cardiac insufficiency, an effort should be made to prevent any recurring endocarditis. Foci of infection should be removed. If syphilis is the basis of this condition it should be treated. If it appears associated with arteriosclerosis, causative factors should be searched out and properly cared for. Although any of these causes may have created irremediable damage, still the amelioration of existing damage and the prevention of further change are most important. During the stage of cardiac decompensation **absolute rest** is indicated and **digitalis** should be used.

If the bronchitis is secondary to rhinitis, pharyngitis, tonsillitis, or sinusitis appropriate special treatment should be undertaken.

When it is secondary to hypertension or chronic nephritis the **diet** must be regulated and directions given the patient regarding the **water intake,** the amount of **salt** to be used, and the care of the **bowel tract.** At times **vasodilators** have a purpose in this group.

When bronchitis is secondary to other pulmonary diseases the treatment of the primary condition again is indicated. If it occurs in tuberculosis, when fever is present, the patient must be put in bed. Out-of-door life and increase of weight are factors of importance in care. For this group change of climate to Saranac, Asheville or Colorado has been found to be of decided benefit.

In those cases associated with bronchial asthma vaccines are sometimes of service and some patients respond well to intrabronchial treatment. Ephraim[31] has had wide experience in the use of adrenalin applied directly to the mucous membrane in this group and believes that it has a place in their therapy.

Pathology.—At the beginning the pathology of chronic bronchitis is similar to that of acute bronchitis, but when the inflammation lasts a long time, or recurs with frequent exacerbations, the deeper layers of the bronchial wall may become involved. The mucous membrane may be thickened and indurated and present a shaggy appearance. This is due in part to a new growth of blood-vessels which pushes the mucous membrane out and gives it its papular look. This has been spoken of as the hypertrophic mucous membrane variety. In contrast to this, as time goes on, connective tissue growth in the bronchial wall is associated with an atrophic mucous membrane, and this may in part become desquamated. As this fibrosis continues the bronchial wall becomes indurated and appears like rigid tubes. These changes affect the walls of the smaller bronchi more quickly than those of the larger, but eventually the whole of the bronchial tree is infiltrated. This diffuse infiltration, or peribronchitis, may extend out into the lung tissue giving an interstitial fibrosis.

Commonly, on account of the weakening of the bronchial wall by inflammation and the strain placed upon it by severe coughing, bronchiectasis may appear. In advanced cases, for similar reasons, emphysema is present and on account of the increase of pressure in the pulmonary circulation hypertrophy and dilatation of the heart occur.

Plastic Bronchitis

Definition.—There is no general agreement as to the name found to be most descriptive of the illness which we are treating here. It appears variously as fibrinous bronchitis, plastic bronchitis, bronchial croup, membranous bronchitis, and pseudo-membranous bronchitis. Whatever name is used, it means that a cast has been formed in some part of the bronchial tree. Until the question of the chemical composition of the cast is finally settled, plastic bronchitis seems to be the most inclusive, and although the least definite is perhaps the most exact. The earliest observers called it bronchial polyp. The name fibrinous bronchitis was given by Remak (1845).

Cases are often reported as acute or chronic, such classification being usually based upon the severity of the syndrome, or upon the association of an acute or chronic disease. Fundamentally this disease syndrome, whether acute or chronic, presents a rather uniform picture, and for our present purpose we shall consider the subject from this point of view. Idiopathic cases have been reported, but they are so rare that they are not here separately grouped as they differ in no essential way from those associated with other diseases.

Etiology.—The disease is comparatively rare. Lebert[32], in 1869, collected 44 cases and to these West[33] added 54 twenty years later. Bettmann[34] collected 98 in 1902, and Posselt[35] 26 more in 1909. Since then the author has found only 8 cases reported.

Casts have been observed at all ages varying from three weeks to seventy-four years. Most cases occur between the second and fourth decade. They are more frequently found in males. Recognizable primary bronchial trauma does not seem to be an etiological factor.

Occupation does not apparently play a definite etiological part, although Pinhini[36] studied 3 cases met with in brick layers working in the neighborhood of a sewer. Patients listed according to occupation include a dock laborer, a grave digger, a blacksmith, school children, housewife, a knife sharpener, and a physician.

Posselt has arranged cases of irritation leading to plastic bronchitis, analyzed from literature, into seven groups, which are as follows: (1) Hereditary tendency, constitutional anomalies, asthma etc.; (2) those of mechanical nature, secretion congestion, dust (especially vegetable dust), soot, smoke, bronchial tubercles, aneurysm, breathing heated air, damp hot smoke, sudden cold air in cool cellars, severe colds; (3) chemical causes,—inhaling gases; (4) poison and infection,—syphilis, gout, obesity, polyarthritis, measles, scarlet fever, typhus, pneumonia, influenza, pulmonary tuberculosis, etc.; (5) cardiac degeneration, heart failure; (6) digestive disturbances; skin and mucous membrane affections,—dermatitis, pemphigus, etc.; and (7) lung edema and acute fibrinous bronchitis after thoracentesis. The last has been observed by a series of authors.

Schwarz[37] thinks that asthma in its increasing fibrinous exudation and clot formation may lead to bronchitis fibrinosa. Posselt states that in those who develop plastic bronchitis from the causes he gives, there may exist a lessened resistance of the bronchial mucous membrane which leads to an abnormal reaction, so that in certain cases plastic bronchitis may occur, while in other individuals with better bronchial mucous membrane resistance, only simple bronchitis appears.

Symptomatology.—There is only one symptom pathognomonic of plastic bronchitis, that is expectoration of a cast from some part of the bronchial tree; and although we may accept any convenient classification of the condition, such as acute, chronic, primary, and secondary, still this one symptom is common to all cases. The delivery of the cast is accompanied by symptoms likewise present in practically all cases. They are paroxysms of coughing, marked dyspnea, expectoration, and fever. These symptoms group themselves so prominently that the patients describe them as "attacks."

The *cough* usually precedes the expectoration for a period of a few hours or as many days. It is apt to be severe, and has been noted several times to simulate the paroxysms of whooping-cough. The attacks continue at intervals until the cast is expectorated, and they practically cease after this.

The *dyspnea* may present an asthmatic character, and in Christian's[38] case it was associated with a sense of oppression through the thorax, as of suffocation or lump in the throat. It is increased at the times of the paroxysms of coughing, and usually ceases immediately upon expectoration of the cast.

Expectoration, as a symptom, depends largely upon the disease with which the plastic exudate in the bronchi is associated. But most of the cases reported describe the sputum as at first of mucous character. Occasionally expectoration is profuse before and during the attack, as in Bettmann's case, and it may become putrid or mucopurulent after the delivery of the cast. Hemorrhagic sputum in varying degrees has been described as occurring at the beginning of the attack, or during the delivery of the cast, or following it. McPhedran[39] states that blood in the sputum usually occurs in one of the three stages of the attack, but since the publication of his article most authors have failed to note this.

Temperature is an habitual accompaniment of the attacks of this disease and ranges from 100° F. (37.88° C.) to 104° F. (40° C.) or 105° F. (40.55° C.). West's[40] chart shows well the relation of the temperature to the delivery of the cast and for that reason is given here. In some of the acute cases temperature has been preceded by chills, as recorded by Bettelheim[41] and Kretschy[42]. In the latter case apparently an acute infection was present which may have accounted for this symptom.

Other symptoms, such as headache, vomiting, pain over the area of the lungs, pain in the epigastrium, are occasionally seen but seem to depend upon the associated illness in which the casts are formed, and upon individual reaction to this illness.

The symptom complex here described recurs in greater or less severity with the expectoration of each cast; in Bettmann's case the patient had these recurrences for six years, and West's patient had seven attacks in four years. In chronic cases recurrences are common, but the cases given by Talley[43] and Shoyer[44] had only one attack each and remained perfectly well thereafter throughout the period of their observation.

Very rarely the symptom complex here described is not found. Holmes's[45] case emphasizes this point. The patient had had a dry hacking cough for eight weeks, present at night and on rising. One morning after a violent paroxysm of coughing she expectorated a phlegm-like mass. There was no dyspnea, and on four recurrences of expectoration of bronchial casts there was no hemoptysis, no sweats, no asthma. The patient could always feel the cast coming from a definite spot on the right side beneath the clavicle.

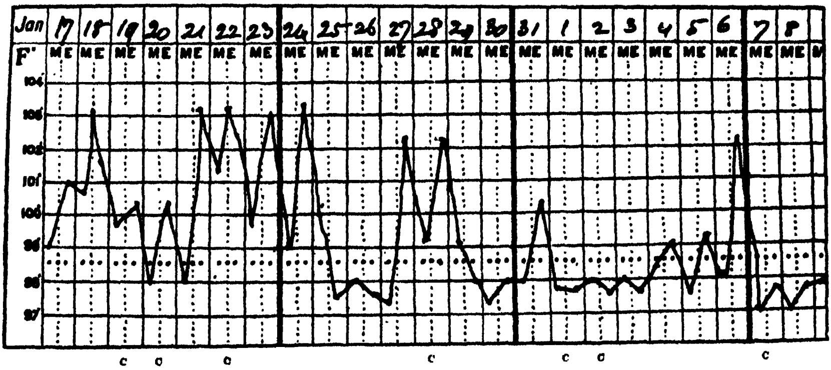

Chart 1. Chart of Temperature Between January 17 and February 8. On Dates Indicated Below Chart by Letter C, Casts were Expectorated. (Reproduced from the original by Dr. Nathan T. Beers.)

Physical Findings.—The physical findings in this condition are not characteristic and only those of bronchial catarrh may be present. This lack of definiteness is apparently due to those associated diseases, during the course of which the bronchial casts are formed. A few cases in which the larger branches of the bronchial tree are plugged give physical findings of bronchial obstruction. Such findings are most frequently at the bases although they may occur at the apices or in the middle lobe of the right side. Landis[46] found deficient expansion of the right base with impairment of percussion note, suppressed breath sounds, and large and small mucous râles. He recognized also a peculiar flapping sound at the end of inspiration,—"ventilgeraüsch" of the Germans, and "bruit de drapeau" of the French. This is a coarse, dry, clicking sound which is caused by a loosened portion of the cast flapping to and fro during respiration. Various authors have described similar signs of bronchial obstruction, more or less marked, which return to normal after the expectoration of the cast. The findings in West's case were rather pronounced and he expressed the opinion that there was a collapse of the left lung subsequent to the occlusion of the left main bronchus; with this the heart was drawn one inch to the left of the left nipple line. Five days after the expulsion of the cast the apex returned to its proper place, although the left lung base showed dull percussion note and absent breath sounds. Apparently these signs are seen only rarely in a pure form, for the physical findings of the primary disease in which cast formation is most often seen, such as heart disease, tuberculosis, asthma, bronchopneumonia, and lung tumor, obscure them.

Description of Casts.—When the cast is expectorated it usually floats in the sputum as a whitish or pinkish mass or ball, and it shows its tree form only when unrolled in water. The casts vary markedly in diameter and length, running from a few millimeters to one and a half centimeters in width, and from a few centimeters to fifteen or more in length. The finer branchings have at times club-like enlargements which have been interpreted as casts of the infundibula. At other times the smallest branches show spiral forms. Sometimes the branches are laminated and hollow, and occasionally there are air bubbles which give the branches the appearance of strings of pearls.

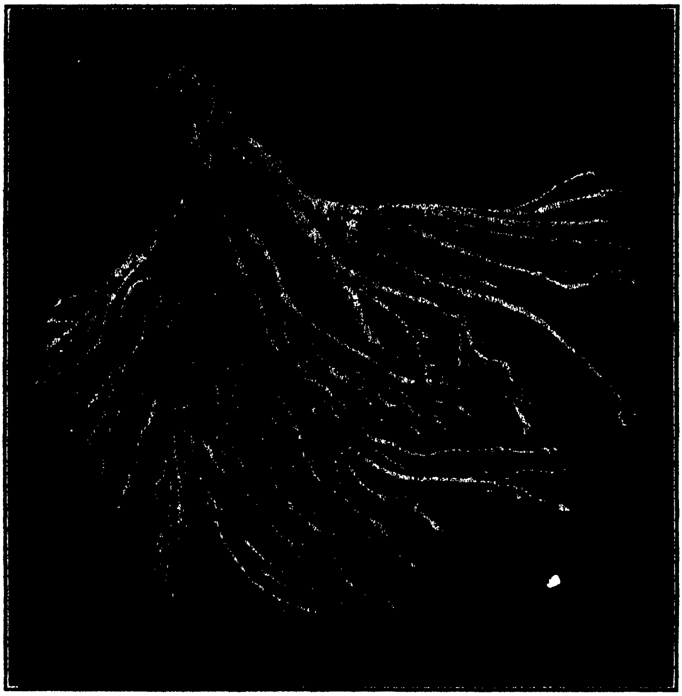

Fig. 1. Photograph of Cast Expectorated. Drawn from a Fresh Specimen. Actual Size Four, and Three-quarters by Four and One-third Inches (Bettmann). (Reproduced from the original by Dr. Nathan T. Beers.)

Hadley[48], in his recent paper, gives an interesting illustration of a case in which the casts were four and one-half inches long, and a quarter of an inch in diameter at the thickest part. He says that about five different casts could be identified, which seemed to show that only five main tubes were affected.

LABORATORY FINDINGS.—Laboratory data is as variable as the conditions with which this disease is associated. The white blood cell-count ranges from 7,000 to 12,000, with from 67 to 72 per cent. leukocytes. Schwarz's[48] case, apparently associated with asthmatic findings, showed a blood eosinophilia of 12 per cent. The sputum varies from mucous to mucopurulent states, and most often shows a mixture of organisms. Those most frequently found are streptococci, staphyloccoci, pneumococci, Friedlander's bacilli, and occasionally the micrococcus catarrhalis and other bacilli. The cells may show mononuclear cytology on the one hand, or a polymorphonuclear or eosinophilic character on the other. Occasional red blood-cells are present. Charcot-Leyden crystals and Curschman spirals have been found in a moderate number of cases, and most often in those associated with asthmatic features. They may occur where there is no clinical evidence of the presence of asthma.

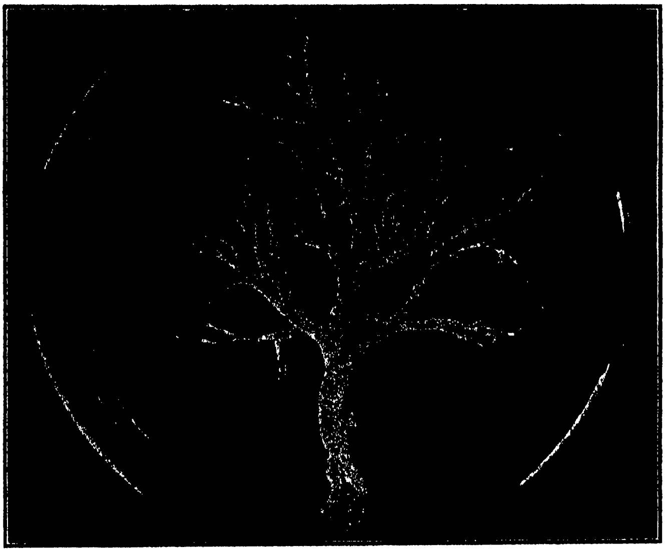

FIG. 2. PHOTOGRAPH OF CAST EXPECTORATED. CASE OF A CHILD FIVE YEARS OLD. ACTUAL SIZE SIX AND A QUARTER BY FIVE AND ONE-HALF INCHES (SCHNEIDER[47]). (Reproduced from the original by Dr. Nathan T. Beers.)

Diagnosis.—The diagnosis can be absolutely made only when the masses expectorated have been investigated and found to be casts from some portion of the bronchial tree. However, this condition is to be thought of when in the course of the diseases above mentioned, with which it is so commonly associated, there occurs a definite paroxysm of coughing, shortness of breath, cyanosis, and fever, and in which the physical findings indicate an obstruction to some area of the bronchial tree, usually basal in position. In such cases we must be suspicious of the presence of this condition.

Association With Other Diseases.—From what has previously been said it will be understood that this illness may arise from many differing pathological states. Bettmann's classification, in 1902, points this out clearly, and most of the cases reported since that time can be reasonably placed in that list. The classification itself is therefore given here.

1. Chronic bronchitis with expectoration of branching casts of the bronchial tree.
2. Acute bronchitis with expectoration of branching casts of the bronchial tree.
3. Cases in which branching casts were not expectorated, but were found in the bronchi at autopsy.
4. Cases in which the casts expectorated showed no dichotomous branching.
5. Expectoration of branching casts in organic heart disease.
6. Expectoration of branching casts in pulmonary tuberculosis.
7. Expectoration of small casts, often non-branching, in association with asthma.
8. Formation of casts in the bronchi in association with pulmonary edema following thoracentesis.
9. Cases whose classification was doubtful because of incomplete reports.

Schnitzler's[49] case is of interest in that the patient had attacks appearing every four weeks in place of suspended menstruation. These attacks disappeared when the menses were reestablished. Bettmann's case occurred with pregnancy, although there was no relation between the former attacks and the menstrual function.

Casts of the bronchial tree have been seen in other conditions but their pathology or bacteriology excludes them from the classification of plastic bronchitis. An example of this is shown in Vintras'[50] patient who expectorated casts apparently occasioned by new growth of the bronchus. Devillers and Renon[51] reported cast-like formation caused by the infection of the aspergillus fumigatus. Finckh[52] pictures such a cast-like body caused by actinomycosis infection.

Treatment.—Treatment must be undertaken from two points of view: First, the removal of the cast; and second, prevention of the formation of the cast. The obscure etiology renders the prevention of recurrences difficult. In those cases occurring in the course of chronic bronchitis, asthma, heart disease, tuberculosis, syphilis, and so on, treatment of the primary disease is often beneficial. Building up the general resistance of the patient must be undertaken. Avoidance of colds, change of climate, and mild climates undoubtedly help. For the removal of the cast **emetics** have been advised, but here the physical condition of the patient must be considered. **Creosote and vapor** continuously inhaled have been recommended by several authorities. It is a question whether the benefit of this does not lie in the loosening effect of deeper respiration, so that the same thing might be accomplished by deep inspiration of pure air. **Arsenic** and **iodid of potassium** have been given internally but without certainty of result. However, Müller[53] claimed that in his case the administration of arsenic restored a normal condition, and when the drug was discontinued recurrences occurred.

Compression of the thorax has been suggested as useful at the time of the attempt to expectorate the cast. Bronchoscopy has not been tried in any case that the author has found in the literature, but possibly in the future it may be undertaken. If the cast lodges at the bifurcation of the trachea, bronchoscopy is definitely indicated, and may prove a life-saving measure.

In those cases associated with asthma, **adrenalin** may be helpful. And for those seen during the course of pulmonary infection **serum** or **vaccine** may be tried. At best the treatment is varied to meet the requirements of each case, but no definite claim can be made for any one.

Prognosis.—Prognosis depends upon the individual findings in each case. Naturally the occurrence of plastic bronchitis in the course of mitral disease would be a definitely more serious condition than its presence in the course of a simple bronchitis.

Fraenkel's[54] analysis of the reported cases of the acute type shows a mortality of 50 per cent. among adults, and 75 per cent. among children. Death comes with evidences of suffocation, in some instances, but may be more gradual, with signs of cardiac weakness or exhaustion, in others. If the severe attacks are overcome, and the illness has not become chronic, recovery follows quickly and completely.

Beschorner[55] noted that the prognosis in the chronic form is far better as regards life, but not for complete recovery. In these cases the attacks may reappear after a few days or months, and sometimes after an interim of several years. Doubt has been expressed as to whether complete recovery has ever been seen in cases of the chronic form of this disease.

Pathology.—That part of the bronchial tract from which the casts arise shows the mucous membrane reddened and swollen, and Kretschy stated that the epithelium was lacking in the places where the clot had been formed. Fraenkel felt that the mucous membrane was primarily traumatized in all cases. This contention has not been borne out by other observers. Rollet[56] found numerous tubercles in the bronchial mucous membrane, and cases of infiltration of the bronchial wall have also been noted.

Much more attention has been paid to the chemical nature of the cast than to the general pathology of the condition. The cast has been found to be composed of fibrin and mucus in varying degrees. Posselt believes that there is a difference in composition of the cast in the acute and chronic forms, and that in the former, in which there are usually asthmatic attacks, the cast is principally mucus and in the chronic forms, with milder attacks, fibrin predominates, although he admits that there are occasional cases which do not fit into this classification. The microscopic character of the cast differs, depending upon its fibrin or mucus nature. In the former there is a hyalin matrix in which there are interwoven fine fibrils often arranged in layers. In these fibril layers cells have been enmeshed; and red blood-cells, polymorphonuclears, eosinophils, and bronchial epithelium are found in all degrees of degeneration. If the structure is principally mucus there are coarser concentric layers which are bound together with small strands and show only a few fine granules throughout the entire substance.

PUTRID BRONCHITIS

Definition.—To Traube[57] is given the credit of being the first to study the clinical aspects of putrid bronchitis. He investigated the character of the sputum of this condition in great detail in his attempt to differentiate it from that of other forms of purulent bronchitis. He felt that it was the result of putrefaction of the exudate occurring in the course of chronic bronchitis. About the same date Dittrich[58] thought that the putrid degeneration of the bronchial secretion was always the result of dilatation of the bronchial branches and hence he felt that there was a primary putrid bronchitis. But he also recognized a sputum of fetid character in many other conditions, such as bronchiectasis, lung abscess, and advanced tuberculosis. In the study of the sputum of the primary type he described the presence of small masses, from millet seed to bean size, yellowish or dirty gray in color, with an extremely foul odor. These he believed to be the feature differentiating this primary type from that occurring secondary to the diseases just mentioned. He thought these masses were the exciting cause of the putrefaction as they were almost exclusively composed of bacteria and putrefactive products, such as fat crystals, free fat, myelin, disintegrating pus, etc. These masses are known as Dittrich's plugs.

Rosenstein[59] (1867) described a case of putrid bronchitis which developed in a young girl after she had inhaled Oïdium albicans; and Canali[60] described a case having actinomycosis of the lungs with markedly fetid sputum. These observations, however, do not justify the assumption that either one of these organisms is the cause of primary putrid bronchitis. Lumniczer[61] and Bernabei[62] each isolated a microörganism which he felt was the cause of the fetor; and Hitzig[63] found two bacilli resembling the colon organism.

Up to the present, therefore, there has been no constant bacterial finding to indicate that any special organism is the cause of this quality of the sputum.

Although the pathology of this condition has been but little reported most of the investigators believe that it is rarely a primary disease but occurs most often in the course of other diseases of the bronchi, such as acute and chronic bronchitis, and most commonly in the latter. What part the bronchi play in that group of lung diseases associated with putrid exudate, such as gangrene, abscess, septic pneumonia, and influenza, has not been settled, but some authorities feel that there may be an associated change in the bronchial secretion which favors this putrefactive process. Marfan's[64] suggestion of gangrene of the bronchi has not been accepted for it does not bear out the pathology of these cases.

Symptomatology.—The most characteristic symptom is that which has given its name to the disease, that is the horribly foul odor of the patient's breath and sputum. This odor is not only nauseating to the patient but permeates the room or even an entire ward. It very commonly simulates that of lung gangrene.

At times the sputum is very abundant. It is always associated with cough; and is usually expectorated with ease. Occasionally there are periodic attacks of cough and expectoration, while at other times these are rather constant symptoms.

The sputum is mucopurulent or purulent and separates into three layers. Fraenkel[65] believes that this is due to the fact that the mucous glands of the bronchi are irritated by the putrefaction and secrete an abundant mucus which becomes mixed with saliva when it is expectorated. After standing, the upper layer is foam-like and is composed of mucus with air bubbles enmeshed in it. Only a few epithelial and pus cells are found in this layer. The middle layer is thin and watery, usually of a dirty color with few formed elements, while the lower contains many organisms, pus cells, and Dittrich's plugs. Fraenkel considers these plugs to be characteristic of the sputum of this condition.

Fever is atypical and lasts usually as long as the putrid expectoration remains. There are cases which run an afebrile course. Occasionally a more severe clinical picture is seen. There may be high temperature associated with emaciation, and the case assumes a serious septic aspect.

Course and Complications.—Whether the condition develops in the course of chronic bronchitis or appears in that group of lung diseases in which the secretions of the bronchi may have become altered, such as lung abscess, gangrene, and bronchiectasis, its duration and course depend principally upon the condition with which it is associated. Although it usually disappears with the primary illness, it may continue after the primary illness has abated. Its occurrence and duration apparently depend in no small way upon the resistance of the patient; in those who are moderately strong the fetid quality may disappear in a week, while in others it may last for months or even extend throughout the entire life of the sufferer. There is a tendency to recurrence.

Gerhardt[66] found joint complications to be the most frequent and of much importance. He noted painful, swollen, inflamed joints with accompanying fever and he felt that these were due to absorption of the putrid bronchial contents. As soon as the expectoration lost its putrefactive character the symptoms quickly disappeared. Pleurisy with effusion, and emphysema have been noted.

Hemoptysis has occurred and is explained as being due to gangrenous destruction following infection extending from the bronchi to the lung parenchyma. Septic metastases occasionally occur in the brain and spinal cord.

Diagnosis.—The diagnosis of this condition is easy on account of the characteristic odor of the sputum. However, such a diagnosis is insufficient since we recognize that there must always be an underlying cause which activated the putrefaction. In any given case two questions are to be considered. Has this putrefaction occurred in the secretion of the bronchial tree which still remains intact? Or has it been superimposed upon conditions involving the lung parenchyma? If the first can be affirmed, we are dealing with a genuine putrid bronchitis. Care should be taken to differentiate bronchiectasis, and this is at times most difficult. In the second instance, lung abscess, tuberculosis, septic bronchopneumonia, and lung gangrene are to be considered as possible conditions upon which this putrefaction may have been grafted.

Bronchiectasis with putrid sputum can be differentiated by a history of previous long-standing lung disease, chronic cough, definite dulness, usually over a base, with physical evidences of exudation in that area, but without tubercle organisms in the sputum.

Lung gangrene and abscess may be recognized by their inclination to hemoptysis and by the finding of shreds of lung tissue with elastic fibers in the sputum.

If fetid sputum appears in the course of unquestioned pulmonary tuberculosis one can assume that there is beginning gangrene in the tuberculous areas or associated tuberculous cavities, and that the character of the sputum arises from a cause other than putrefaction of the bronchial contents.

Treatment.—In that group of cases in which this condition is superimposed upon an acute or chronic bronchitis those measures which aid in building up the general condition of the patient, such as **increasing the nourishment, tonics,** and **open air,** are beneficial. **Creosote** taken internally or by **steam vapor** may diminish the odor which is so distressing to the patient. Endobronchial treatment with **terpinol** and **menthol** has been used by Ephraim[67] and in selected cases may yield gratifying results. In those cases which arise from the other conditions considered, treatment must be directed to the underlying cause.

TRACHEOBRONCHIAL SYPHILIS

Definition.—The recognition of syphilis as a cause of bronchial disease has been ascribed to Munk (1841). In his case there was ulceration of the soft palate with many minute ulcers in the mucous membrane of the larynx as well as many ulcers in the smaller bronchi. Since this initial observation many investigators have identified lesions in various parts of the upper respiratory organs in addition to those found in the bronchial system. Conner[68] tersely says that a separation of the cases of syphilis of the trachea from those of syphilis of the bronchi cannot be made with propriety since both, in their clinical and their pathological aspects, seem identical, and since both are so commonly found associated in the same subject. So many others concur in this opinion that we accept tracheobronchial syphilis to be a most fitting term by which to define this condition. The name phthisis syphilitica has been given by some writers to those cases in which the symptoms are those of hectic fever rather than of bronchial stenosis.

The primary lesion of syphilis has not been found, up to the present, in the trachea or bronchi. There are a few recorded cases of secondary manifestations in this tract, but they have been unattended by any clinical picture. Therefore, we will confine ourselves, in our discussion here, to the tertiary and hereditary lesions of syphilis occurring in the trachea or bronchi.

Symptomatology.—Gerhardt[62] in his analysis of 22 cases grouped the symptoms into three stages: (1) Stage of irritation; (2) stage of stenosis; and (3) stage of suffocative attacks.

After a most careful digest of the subject Conner feels that the cases reported since that time can reasonably fall into this grouping and from his study he works out the symptoms of these stages in a way to conform to the following table:

(1) Stage of irritation	cough	continuous	dry
			expectoration
		paroxysmal	
	expectoration	mucous	
		mucopurulent	
		blood stained	
	hemoptysis		
	dyspnea		
(2) Stage of permanent stenosis	stridor		
	dyspnea	constant	
		paroxysmal	
(3) Stage of suffocative attacks	air hunger		
	cyanosis		
	tachycardia		
	unconsciousness		

Gerhardt's Classification of Stages with Symptoms as Further Determined by Conner's Study of 128 Cases in the Literature.

The *first or irritative stage* is characterized by cough, expectoration, hemorrhage, and dyspnea. *Cough* is rarely absent and usually appears as the first symptom, remaining as a prominent complaint throughout the course of the disease. It may be a dry hacking cough and continue to be so or it may be accompanied by expectoration. Occasionally it is paroxysmal and may be harsh or brassy in type.

Expectoration occurs in about 40 per cent. of the recorded cases and varies individually, also assuming different characters at different times. It may be mucous, mucopurulent, blood-stained, etc. Portions of the bronchial wall may be expectorated at intervals. Emanuel's[70] patient expectorated a necrotic mass containing three rings of tracheal cartilages.

Frank *hemoptysis* occurred in 8 of the 82 cases collected by Conner. Necropsy showed that this was due to the syphilitic process perforating a large blood-vessel, usually a bronchial artery or the aortic arch.

Dyspnea was the most common of all symptoms and it was usually associated with some stage of bronchial stenosis. Occasionally it was the first symptom complained of and in 12 of Conner's list it occupied the foreground of the clinical picture and was most distressing and alarming. Plicque[71] noted that the intensity of the dyspnea was often out of all proportion to the local lung signs, and that the patients otherwise showed remarkably good general health.

The symptoms of this irritative stage vary in duration from a few months to a year and occasionally cover a period of two or three years. Bouchut[72] noted that his patient had a chronic cough for thirty-two years, and this was associated with expectoration for twelve years. Denker's[73] patient had a cough for six years, which condition was associated with expectoration and intrathoracic pain.

The *second stage*, that of *bronchial stenosis*, is associated with stridor and dyspnea. The most individual sign of bronchial stenosis is *stridor*. This has been observed in about 50 per cent. of the cases and may either be inspiratory or expiratory in time. It is, however, of loudest intensity during inspiration and in many instances has been noted as occurring in inspiration alone. It may be present rather continuously or occur only at the times of paroxysmal attacks of difficult breathing. This sound has been variously described as roaring, whistling, or squeaking. It varies in intensity from a noise so loud that all the patients in the ward can hear it to one that is just audible, occurring only after exertion. This sound does not seem to depend upon the location of the stricture, for it is heard when one as well as both bronchi are narrowed and whether the narrowing in the tract be high or low.

Dyspnea may be a constant symptom or it may occur in paroxysms. There is scant accurate description as to whether in the early stage the dyspnea is inspiratory or expiratory; but when the stenosis becomes associated with stridulous breathing the inspiratory effort is predominant and the dyspnea becomes more distinctly of the inspiratory type.

The paroxysmal dyspnea appears in about half of the cases reported at some time in the course of the bronchial obstruction and ushers in the *third stage* with its *suffocative attacks*. It is due not only to interference with respiration but to associated cardiac insufficiency. The attacks are usually brought on by exertion, such as running or coughing, but occasionally occur without any apparent cause. Certain cases have paroxysmal attacks in the night. They are truly described as suffocative and are associated with air hunger, cyanosis, tachycardia, and patients may even become unconscious and pulseless. Occasionally there is at this time an inspiratory retraction of the tissues of the neck and epigastrium.

Now and then other symptoms have been present. Pain of a dull constricting nature behind the sternum has been noted. Sometimes it is in the trachea. Not infrequently the voice is affected. It may be weak, absent, or similar to that in recurrent laryngeal paralysis. Cases of voice change have been observed in which the syphilitic lesion was in the trachea and bronchi, and the larynx was perfectly normal.

Fixation of the larynx during respiration was noted by Gerhardt in cases associated with tracheal stenosis. He laid much stress upon this but many observers since that time, who have particularly noted the point, have failed to confirm his observation.

Physical Findings.—There is no well-recognized group of physical findings in this disease. This is to be expected, for the disease runs through various stages which are associated with its changing pathology.

In the irritative stage the physical findings may simulate those of chronic bronchitis. As the disease advances they may become like those of asthma, as in the case described by Arrowsmith[74], in which inspiration was labored and rapid and expiration was prolonged and ended in a grunt. From such findings many cases have at first been interpreted as those of bronchial asthma. Wadsack[75] reports that in one of his cases the accessory muscles were used and the supraclavicular fossæ were drawn in and the head bowed forward. The lung bed was hyperresonant and a vesicular murmur was heard throughout. His second case showed the lung borders not increased but a full resonant note was present. In both cases there were moist and sibilant râles.

Certain cases show marked emaciation and some of them have symptoms of superadded pulmonary infection, making a picture closely resembling chronic tuberculosis.

During the attacks of dyspnea, and particularly those of the paroxysmal type, physical findings become more uniform and worthy of attention. Inspiration is longer and more difficult than expiration and with this there is commonly retraction of the suprasternal, supraclavicular, and epigastric regions. This retraction, when present, is the most striking physical feature of the dyspnea.

Although, as stated, the physical findings are not conclusive alone, tracheoscopy and bronchoscopy contribute additional valuable information. The bronchoscopist, in any given case, cannot assert positively that the ulcer, tumor, or stricture is syphilitic, but he locates the anatomical cause of the symptoms enumerated, and stimulates the attempt, whether by therapy or other means, to establish its syphilitic nature. Occasionally the bronchoscope reveals such characteristic lesions that the observer hazards an opinion as to the nature of the obstruction. In one of Kahler's[76] cases he describes a tumor mass extending from the back and lower wall of the bronchus, 2 cm. (.7874 in.) below the bifurcation. It was dusky-red, smooth, half spherical, and nearly closed the bronchus, and had at the summit a sharp-edged, bean-sized, yellowish-white growth. The entire bronchial wall was red and appeared to be infiltrated. He expressed the opinion that it was a gumma of the left bronchus, and stated that such characteristics are typical of this condition and hardly need a Wassermann reaction for confirmation.

Diagnosis.—In the irritative stage, with the symptoms and physical signs of bronchitis only, there may be little to attract the attention to syphilis as the cause of the illness. But if the patient shows severe manifestations of tertiary syphilis, has a cough, expectoration, with dyspnea extending over a period of several months to as many years and increasing in severity as time passes, we should at least be suspicious of syphilitic disease of the trachea and bronchi. This suspicion should be increased if repeated sputum examination fails to find tubercle organisms, and there are no physical or radiographic findings of localized pulmonary tuberculosis or tumor masses arising from the mediastinal or pulmonary structures, such as aneurysms, mediastinal tumors, enlarged glands, etc.

If in addition to this data laryngoscopic examination shows ulcers or scars of the pharynx or larynx, syphilis may be ventured upon as the etiology of the condition, leaving little reasonable doubt, and this in turn may be cleared up if the Wassermann reaction is positive.

When the stage of obstruction to breathing appears, more information is necessary to answer the questions as to where the obstruction is situated and of what it is composed. The tracheoscope and bronchoscope will answer the queries concerning the location and nature of this obstruction.

Associated Lesions.—It has already been said that this condition is most often seen in cases showing severe tertiary manifestations of syphilis. Conner's tabulation shows the larynx involved in 12 per cent., the lesions there being of the nature of gummata or scars. Twenty per cent. of the cases in his list show similar lesions in the mouth, nose, and throat. In the terminal stages of the disease many cases present clinical pictures of either broncho- or true lobar pneumonia. These are secondary to the primary bronchial obstruction. Conner's own case illustrates this well. Dilatation of the trachea or bronchi occurs with surprising infrequency, for in the 97 cases which Conner analyzes, dilatation occurred above the stricture in only 3 cases and below it in only 9.

Bronchiectasis is at times found below the point of obstruction. Pleural effusions may exist and complicate the findings of bronchial obstruction. Pitt[77] observed this in 2 of the 7 cases in his series of autopsies. Occasionally old tuberculosis or associated emphysema are present, and Emanuel noted the presence of gummata on the foot. Hoffmann[78] found acute lung edema as a terminal condition associated with this disease. Possibly this is of circulatory origin or in some way due to the numerous areas of bronchial ulceration.

Treatment.—Treatment falls under two heads: first, specific medication; second, mechanical manipulation, in a few selected cases. The specific treatment includes the use of **mercury, iodid,** and **salvarsan** or some of the other **arsenic preparations** and is to be instituted irrespective of the stage of the disease. Patients with hard cicatrices have shown surprising improvement under this treatment, which is apparently due to some change occurring in the infiltration of the bronchial wall. Early cases and those with the findings of ulcer or small gummata respond astonishingly well. Halle's[79] case with gummata of the bronchus demonstrates this; in 14 days from the beginning of intravenous arsenical treatment the entire gummatous growth disappeared In these cases associated with tuberculosis, or in which there is suspicion of gummatous infiltration in the large blood-vessels of the mediastinum, iodid and salvarsan must be used with great caution, since they may increase the local congestion and thereby tend to spread the associated tuberculosis or hasten an impending ulcerative perforation. In such cases mercury is the drug of election and is best used in inunction. Mayer[80], quoted by Plicque, believes that exposure to **x-ray** is an effective aid in treating gummatous or diffuse bronchial infiltration types of stenosis, but says that they have no effect on complicating bronchiectasis. In the latter case he notes that surgery is disastrous. Even in those cases reported lately little is said of the use of mechanical treatment in cases of fibrous intrabronchial obstructions. However, Reede[81] recognized that such strictures could be relieved by the method of bronchoscopic dilatation practised previously rather successfully by Marcus[82] and Halle.

Prognosis.—Prognosis depends largely upon the clinical stage in which the condition is recognized. The small gummata or early ulcers give much better prognosis than do those cases associated with stricture from scar formation, or those complicated by secondary lung infection such as tuberculosis or bronchiectasis. Certainly if the cases were recognized early the prognosis would be distinctly better than is indicated by analysis of the statistics of the past. In Vierling's[83] list (1878) of 46 patients, 39 died; 3 were cured; and 4 improved. In Conner's list of 82 patients (1903), 24 were cured or improved and 58 died. These are rather discouraging figures when we consider the usual response of syphilitics to specific treatment. Apparently they are due to lack of early recognition of the disease, for most investigators feel that specific treatment, when undertaken quickly, easily assures a good result, sometimes to the point of seeming miraculous.

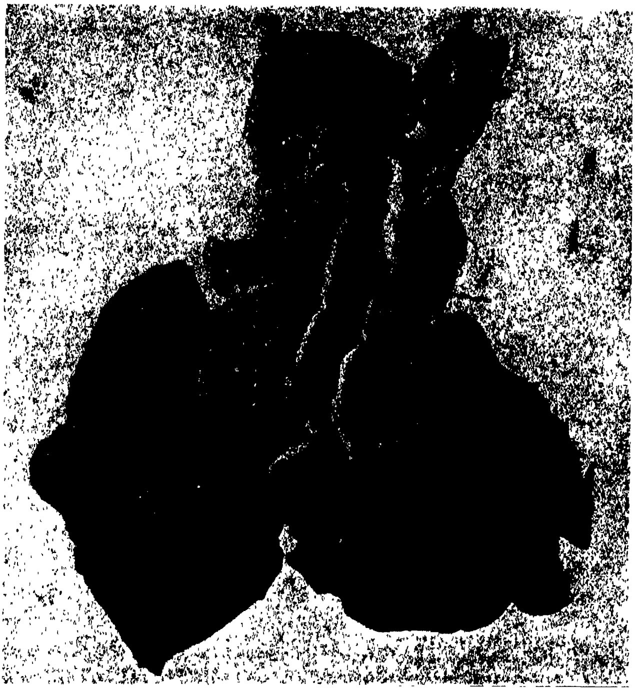

FIG. 3. FROM WADSACK. SHOWING ENDOTRACHEAL INFILTRATION AND FIBROSIS, WITH MARKED NARROWING OF BOTH PRIMARY BRONCHI DUE TO SYPHILIS.
(Reproduced from the original by Dr. Nathan T. Beers.)

In the advanced stage of the disease when suffocative attacks of dyspnea appear, or when the patient is markedly exhausted or has an associated bronchiectasis, the prognosis is extremely grave and many of the cases terminate from an associated bronchopneumonic infection.

Pathology.—Acquired tertiary syphilis of the bronchi may appear early or late. The shortest time recorded was nine months after infection and the longest 42 years. Conner found the disease occurring on an average of 10 years after the primary lesion, in 31 cases where this point could be determined, and he noted that the cases of inherited syphilis developed the bronchial complication, on an average, at about 10 years of age.

The lesions of tertiary syphilis, gummata, ulcers, or cicatrices appear singly or in combination and are most frequently found at the lower end of the trachea or at the bifurcation. They may appear in one or both larger bronchi and in the smaller bronchial tubes. Gummata appear as single or multiple, small or large reddish masses projecting in varying degrees into the lumen of the bronchi. Or they may occur as infiltration involving the whole or any part of the bronchial wall invading even the cartilages. This lesion appeared in 14 per cent. of the cases tabulated by Conner. Ulcers were present in 44 per cent. of the list. They may be single or multiple and were usually large and showed deep infiltration. Perforation of an ulcer base may occur either in the mediastinum or in some large blood-vessel. In the former, abscesses or emphysema may develop, while in the latter hemorrhage, occasioning sudden death, may occur. Infrequently perforation has taken place in the esophagus.

Scars develop as a result of the above syphilitic changes and appear as stellate figures or as dense, hard bands of tissue projecting in various directions into the lumen of the tube. At times these bands are like diaphragms.

In all the lesions mentioned above the bronchial wall is involved in varying degrees of infiltration. Hoffmann believes that in addition to these circumscribed lesions and infiltrations there is a diffuse infiltration of the bronchial wall in which the mucous membrane becomes enormously thickened, the epithelium is lost and the tissue beneath it is changed into thick, hard, connective tissue in which there are many round cells. As time goes on this cell infiltration disappears, the connective tissue shrinks and endobronchial or endotracheal obstruction results. This dense connective tissue scar may encircle the entire bronchus or distort it in such a bizarre manner that the narrowing shows the most varied forms.

Not infrequently the tracheobronchial glands become enlarged and give rise to recurrent laryngeal nerve palsy or symptoms of compression stenosis.

NEW GROWTH OF THE BRONCHI

Definition.—For some time pathologists have distinguished between primary tumors of the lung parenchyma and those having their origin in the bronchi. They have even classified their cases on such a basis. Pässler,[84] following this classification, recognized the difference in symptomatology in these two conditions but did not emphasize it. More recently

Weller[85], in his article on primary carcinoma of the bronchi, analyzes the previously reported cases and presents a syndrome of symptoms and physical findings which he feels should aid not only in recognizing this type of growth but should facilitate its earlier detection. Certainly this seems logical and is a step forward.

Up to the present no one has attempted to formulate a clinical syndrome diagnostic of primary benign growth of the bronchi, but in our study of such cases in the literature we are convinced that they present the same clinical picture, with the exception of the occurrence of metastases, as that of the malignant growths; they demand the same diagnostic procedures, and give rise to the same complicating sequellæ as those of the primary malignant disease, hence we have included the two types of growth in this article.

Etiology.—This condition is not peculiar to any occupation and all social classes are included in the cases reported. Wolf[86] thinks that possibly scar formation from previous luetic infection or other causes may predispose markedly to this condition. He likewise mentions a breaking through into the bronchi of hard enlarged bronchial glands and considers that soot and dust from these may act as tissue irritants leading to slow, continued, inflammatory change. It has been found that males are more often affected than females. Adler[87] explains the preponderance of cases in the former as due to occupations and habits which irritate the bronchial mucous membrane to a greater extent than do those to which women are commonly exposed. Occasionally trauma has occurred before the onset of the symptoms and is held as a possible etiological factor. However, its importance in a series of cases can be properly estimated by Weller's analysis which showed that it had a possible bearing on only 3 of the 89 cases abstracted. Although tuberculosis was present in 11 of these cases, and may be found associated with peri-bronchial changes, most pathologists do not consider it a definite causative factor. But there are recent observers who feel that this association may be of more importance than has previously been recognized.

Symptomatology.—Although Weller's article deals only with primary carcinoma of the bronchi, his tabulation of symptoms and physical findings is so complete that it will be freely quoted here. He gives the symptoms found in his series in their order of frequency as cough, dyspnea, expectoration, hemoptysis, thoracic pain and certain pressure manifestations.

The *cough* has an insidious onset and is the most common symptom. It may be a dry, hacking type, constant, or paroxysmal. Jackson's[88] case describes the cough as one occurring with a heavy cold, while Spiess's[89] patient had such severe coughing as to be associated with vomiting. Almost all commentators have observed that the cough was increased when the patient was exercising.

Dyspnea is also a very common symptom and increases in severity as the disease progresses. There may be a feeling of obstruction to breathing or compression of one side of the lung during the attacks of shortness of breath, and Jackson's patient described a ball-valve shutting off of the breath. Pitt's[90] patient had an increasing dyspnea of three years which gradually became associated with stridor which was most marked when he lay on the left side.

Expectoration of mucoid or mucopurulent sputum may be associated with the cough or dyspnea. Most authors, reporting recently, lay stress upon recurring hemoptysis, and Ephraim's[91] case of only three weeks' illness presented this as the first and only symptom. In Weller's analysis hemoptysis was described in some degree in 35 of the 42 cases in which this symptom was mentioned, and he calls attention to the fact that various observers have not noted the raspberry-jelly type of sputum which previously has been thought to be so distinctive of new growth.

Although Adler gives a dull pressure pain as the most common of all symptoms of primary new growth of the lung, Weller's data does not show it to be the most common in primary new growth of the bronchi. When it is present it is variously described as a compression sensation or tightness of the chest and is commonly referred to the side involved. At times the pain may be stabbing in nature or it may be increased by coughing or bending. Jex-Blake's[92] patient showed the position influence on pain to such an extent that she was most comfortable when she was standing erect or lying flat. Occasionally the pain is referred to a breast, an arm, or the back. Weller groups his pressure symptoms as due to the neoplasm invading structures of glands secondarily, and emphasizes their great diagnostic value. In 5 of the 89 cases studied there was recurrent laryngeal paralysis; difficulty in swallowing was noted in 4 cases; and superficial venous distension of one arm and of the head was noted 9 times.

The duration of the symptoms varies from a few months to several years. Fraenkel[93] remarked that at the beginning of the disease the general health of the patient was usually good; while Pässler stated that cachexia is common in the later course of disease and occasionally is the first symptom to appear.

Physical Findings.—The physical findings of primary new growth of the bronchi are those of bronchial obstruction and they vary with the degree of the obstruction. Jackson's and Nesbitt's[94] cases showed these findings sufficiently clear for an opinion of bronchial obstruction to be ventured upon. In the former case there was retraction of the right side of the thorax with an impaired percussion note over the same area. The respiratory sounds were suppressed. In the latter case expansion and fremitus were diminished over the left side; the note was less resonant than over the corresponding right side, and there was a complete absence of breath sounds. Signs of bronchiectasis may appear and not a few observers have expressed such an opinion, from the physical findings, only to be shown at necropsy that it was purely symptomatic of the bronchial stenosis. Occasionally stridulous breathing is observed. As the tumor enlarges and invades the surrounding lung or mediastinal tissue, complicating physical signs may appear. Scott and Leist[95] described a pleurisy over the lower half of the affected lung. Occasionally pleural effusion has been a complicating finding. Recurrent laryngeal paralysis, difficulty in swallowing, loss of voice, and so on have been noted as signs of mediastinal pressure. Nesbitt found paralysis of the left diaphragm which he explained as due to pressure upon the phrenic nerve as it passes through the mediastinal space.

Fluoroscopic examination is a valuable assistance at times in verifying the physical findings already enumerated. Dr. George Johnson, in fluoroscoping Jackson's patient, found a trefoil-shaped shadow beginning an inch below the bifurcation and extending downward over the whole right base. This shadow was so dense that even the diaphragm stand could not be distinguished and gave the appearance of an unresolved pneumonia. Two days later portions of this had cleared up. It was considered that it had been due to atelectasis dependent upon obstruction of the right bronchus. Diagnostic bronchoscopy was strongly urged and a tumor was discovered as the cause of the obstruction. When the tumor becomes enlarged the x-ray offers much greater help than in those cases in which the growth is early and has remained within the bronchial wall. In the former instances Posselt[96] feels that it stands first as a diagnostic aid, for it not only locates the tumor but pictures the irregular-edged, mottled shadow characteristic of new growth.

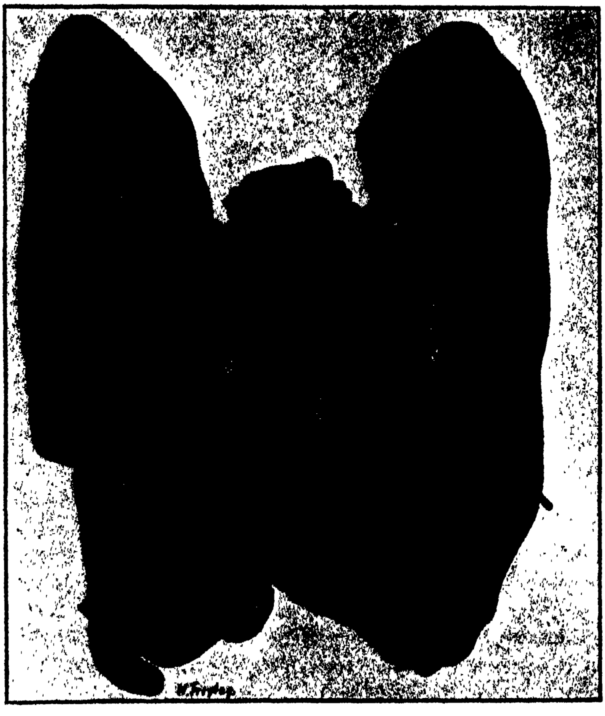

Fig. 4. From Kirch. Showing Polyp of the Left Primary Bronchus with Resulting Bronchiectasis Lung Change.
(Reproduced from the original by Dr. Nathan T. Beers.)

For the absolute recognition of bronchial growth the bronchoscope gives us the most definite data. Most of these growths are found in the larger bronchi of which field the bronchoscopist has direct vision.

Diagnosis.—A study of the cases recorded establishes the fact that most of them were diagnosed only at necropsy. Many of the cases interpreted clinically as bronchiectasis, gangrene, or chronic pneumonia were, at that time, found to be secondary to the primary disease. Kirch[97] states this well by saying that the autopsy of his case established the clinical diagnosis of fetid bronchitis and suspected pneumonia of the left side. But in addition it brought to light an astonishing discovery, for in the left primary bronchus an acorn-sized polyp sprang from the wall and, although the patient had been complaining of symptoms for a period of only three months, still there was a high degree of bronchiectatic formation and severe lung changes below the point of obstruction.

More recently, with the increasing use of bronchoscopy, many observers have not only confirmed their diagnoses of new growth, but with its help they have attempted removal with unusually good results.

Although the condition is not a common one, still it should be thought of as a possibility in any patient presenting symptoms of cough, dyspnea, expectoration, and hemoptysis. If, in addition, there are physical signs of some degree of bronchial obstruction or of monolateral asthma or bronchitis, diagnostic bronchoscopy is indicated. In addition to the foregoing criteria for the employment of bronchoscopy, Jackson feels that even in suspected cases of tuberculosis, where persistent search fails to find the organism it should be part of the examination. In this way will the primary condition be observed before the serious secondary complicating features have appeared. However, the onset of bronchiectasis or chronic pulmonary inflammation does not exclude bronchoscopy nor invalidate the good which may result from its use. Knack,[98] after the study of one case, utters a warning not to neglect bronchoscopy in all cases of bronchiectatic formation, for he considers that many of these may be due to small tumor masses which may admit of the opportunity of removal and thus save the life of the patient.

Much has been written concerning the value of the sputum examination for the diagnosis of this condition, but apparently very few cases have given findings which are conclusive. Wolf[98] thought that tumor particles seldom appear, for the reason that they are so changed by putrefaction before they are expectorated that they are not recognizable. Posselt calls attention to the presence of hemorrhagic sputum associated with an increasing cachexia with signs of stenosis and believes that this should stimulate one to investigate primary bronchial growth as its cause. Gerhardt felt that the hemorrhagic sputum of old persons should place them under suspicion of having bronchial carcinoma.

It has been attempted in the foregoing to lay special stress upon the diagnostic aids for the early recognition of primary bronchial new growth, and in this early recognition the x-ray does not play as important a rôle as has been previously ascribed to it. Certainly, at the beginning of the growth little can be expected to show by radioscopy. Later, as the bronchial wall or glands become involved its aid cannot be overestimated. For it not only locates the size, form, and position of the tumor but helps in differentiating those border-line conditions which so often give us great difficulty. Posselt has summarized its use remarkably well in the following: "The more frequently the site of primary development occurs in the small bronchi so much more will the appearance recall chronic inflammatory parenchymatous and neoplastic processes of the lung parenchyma. The more frequently carcinoma occurs in the larger bronchi so much more, for diagnostic purposes, must mediastinal processes be excluded, such as lymphosarcoma, malignant granuloma gummata, and aortic aneurysm."

Prognosis and Treatment.—The prognosis depends entirely upon the variety of the growth. The benign type may be removed by the **bronchoscope,** and the patient return to perfect health. Such was the result in Spiess's case. In the event of malignant tumors, early recognition is imperative if favorable results are to be expected. Certainly, little in a curative way can be hoped for after the lung parenchyma or bronchial glands have become involved. Recently Jackson, operating with the bronchoscope, removed a histologically malignant endothelial tumor from the right bronchus and the patient had remained perfectly well for a year and a half at the time the case was reported.

Up to the present time only a few attempts have been made to remove malignant disease with the aid of the bronchoscope, but with the earlier recognition of bronchial new growth this method bids well to gain in favor. Possibly with the refinements of radium therapy another weapon may be added with which to fight this once hopeless condition.

Pathology.—Both benign and malignant tumors may arise from the bronchi. Rokitansky[100] found a lipoma which almost filled the lumen of the left bronchus. Spiess found the right bronchus completely closed by an edematous polyp which showed areas of cartilaginous nodules. Enchondromas were observed by Siegert[101] and Blecher.[102]

Malignant tumors of the larger bronchi which passed the scrutiny of microscopical examination are found more commonly in males than in females in the ratio of 4 to 1.

The larger bronchi are apparently the preferred seat for the development of new growth. From his study Wolf believes that malignancy never developed in the fine branches of the bronchi but always immediately below the bifurcation in one of the principal bronchi and from that site constantly involved the bronchial glands. From 23 cases studied microscopically by him he found pavement cell cancer eight times and cylindrical cell carcinoma seven times, but he feels that in spite of his own experience the majority of bronchial cancers are the cylindrical cell variety, with their point of origin in the bronchial mucous membrane or the bronchial mucous glands.

In 89 cases Weller could classify 22 as having their origin in the glands, while 17 arose from the bronchial mucosa. The point of origin of the remaining 50 seemed uncertain to him.

Metastases occur very frequently from primary bronchial carcinoma. Wolf first mentioned this after a study of 23 cases and found 21 showing metastases. He considered that this was due to the bronchial carcinoma invading the bronchial glands at an early time. Weller's study noted metastases 70 times in 89 cases. Although the location of secondary growths may be most varied, there is a tendency to brain and lymph-gland metastases. Twelve cases of the former were listed in his series and in some of these the clinical picture of the illness was dominated by these secondary involvements. The lymph glands were involved in 13 cases and were cervical, supraclavicular, or axillary. He remarked that if the lymph glands of one side only were involved, the new growth probably involved the bronchus of the same side.

More rarely may sarcoma be found primarily in the bronchial wall. Such a case is reported by Ephraim. A small spindle cell sarcoma and a spindle cell hemangiosarcoma are recorded by Jex-Blake.

REFERENCES

Acute Bronchitis

1. HOFFMAN. Die Krankheiten der Bronchien, 1896.
2. VAUGHAN AND PALMER. Communicable diseases in the United States. Army Mil. Surgeon, Oct. 18, 1918, xliii, 392.
3. SOPER. Bronchitis the most significant disease of the war. Bost. Med. and Surg. Jour., July 24, 1919, clxxxi, 95.
4. EMERSON. The experience of the American Expeditionary Force with respiratory infections. War Med., Oct., 1918, ii, No. 3, p. 311.
5. ZINSSER. Acute respiratory infections. War Med., Oct., 1918, ii, No. 3, p. 316.
6. PFEIFFER. Vorläufige Mittheilunger über die Erreger der Influenza. Deutsche Med. Wchnschr., 1892, xviii, 28.
7. LORD. Infections of the respiratory tract with influenza bacilli and other organisms, their clinical and pathological similarity and confusion with tuberculosis. Bost. Med. and Surg. Jour., May 11 and 18, 1905.
8. FRAENKEL. Spezielle Pathologie und Therapie der Lungenkrankungen, 1904.
9. MARFAN. Maladies des Bronches. In Traité de Médicine, Charcot, Bouchard et Brissaud, 1893, IV, p. 287.
10. EWART. In System of Medicine, Ed. T. C. Albutt, VI, 1899.
11. VOORHEES. A successful treatment for acute infections of the air-ways. Bost. Med. and Surg. Jour., 1915, clxiii, 702.
12. ARMSTRONG AND GOODMAN. The excretion of salicylic acid and hexamethylenamin in the sputum. Jour. A.M.A., May 27, 1911, p. 1553.
13. HEITMULLER. The excretion of hexamethylenamin. Jour. A.M.A., April 9, 1919, p. 1222.
14. MILLER. Hexamethylenamin: A remedy for common colds. Jour. A.M.A., June 10, 1911, p. 1718.
15. VANDERHOOF. Hexamethylenamin in the treatment of bronchitis. Jour. A.M.A., Feb. 3, 1912, p. 331.
16. NEVES. L'Urotopine dans les bronchitis. Archives de médicine des infants, January, 1918, xxi, No. 1, p. 29.
17. BLUM. Iodin a specific germicide in respiratory affections. Calif. St. Jour. Med., 1914, xii, 207.
18. SEIBERT. Camphor and pneumococci. Med. Rec., April 20, 1912, lxxxi, 750.
19. DELAVAN. The value of dichloramin-T chlorcosane solution (Dakin-Dunham) in the treatment of infections of the upper air passages. Boston Med. and Surg. Jour., 1918, clxxix, 677.
20. MINCHEW. Prophylactic treatment of diseases of the respiratory tract. Mil. Surgeon, 1918, xliii, 362.
21. BADHAM. Observations on the inflammatory affections of the mucus membrane of the bronchæ, 1808.

Chronic Bronchitis

22. Hoffmann. Die Krankheiten der Bronchien. 1896.
23. Fraenkel. Spezielle Pathologie und Therapieder Lungenkrankungen. 1904.
24. Lord. Diseases of the bronchi, lungs, and pleura. 1915.
25. Jackson. Endothelioma of the right bronchus removed by preoral oronchoscopy. Am. Jour. Med. Sci., 1917, cliii, 471.
26. Bowen. Unsuspected foreign body as frequent cause of chronic bronchitis. Am. Jour. Roentgen, vi, No. 3, 111.
27. Mantoux. La bronchite chronique puré. Les enseignements de la guerre. Progrès Méd., Nov. 8, 1919, xxxiv, 445.
28. Eyre and Lowe. Prophylactic vaccinations. The Lancet, Oct. 12, 1918, ii, 484.
29. Babcock. Autogenous vaccines in the treatment of bronchitis and asthma. The Lancet-Clinic, Feb. 12, 1916, cxv, 139.
30. Robinson and Queen. Autogenous bacterial vaccines in bronchitis. Southern Med. Jour., Oct., 1916, ix, 864.
31. Ephraim. Über die Wirkung des Adrenalins beim Asthma bronchiale und bei der chronischen Bronchitis. Deutsche med. Wchnschr., 1912, xxxviii, 1453.
32. Lebert. Über das Vorkommen Fibrinöser Entzündungs products in den Bronchien und Lungen-Alveolen. Uber fibrinöse oder pseudomembranöse Bronchitis und Pneumonie. Bronchitis fibrinosa, Bronchitis pseudo membranacea, Pneumonia fibrinosa. Deutsche Arch. für klin. Med., 1869, Bd. 74.
33. West. Plastic bronchitis. Practitioner, 1889, cliii, 83.
34. Bettmann. Report of a case of fibrinous bronchitis, with a review of all the cases in the literature. Am. Jour. Med. Sci., 1902, cxxiii, 305.
35. Posselt. Chronische Bronchialerkrankungen mit Ausschluss der Tuberkulose. V. Bronchitis plastica. Medizinische Klinik, 1909, Nr. 33, 1222 and 1258.
36. Pinhini. Contributo allo studio della bronchite fibrin, acuta primitiva. Riv. clin. Arch. ital. di Clin. med., 1889, p. 150.
37. Schwarz. Zur Pathologie der fibrinosen Bronchitis. Wien. med. Wchnschr., 1908, lviii, 1177, 1284, 1307.
38. Christian. Fibrinous bronchitis. Med. Clinics of N. America, 1919, ii, No. 5, p. 1255.
39. McPhedran. In Osler, Modern Medicine, 1907, III, 675.
40. West. Plastic bronchitis. Lancet, Feb. 15, 1908, p. 489.
41. Bettelheim. Casuistische Mittheilung über Bronchitis fibrinosa. Schmidt's Jahrbücher, 1873, clxiii.
42. Kretschy. Zur Bronchitis crouposa acuta. Deutsch. med. Wchnschr., 1883, No. 8; and Wiener med. Wchnschr., 1873, Nos. 14, 15, and 16.
43. Talley. Acute fibrinous bronchitis with report of case. Old Dominion Jour. Med. and Surg., 1908, vii, 96.
44. Shoyer. Fibrinous bronchitis. Brit. Med. Jour., Oct. 20, 1906, p. 1035.
45. Holmes. A case of fibrinous bronchitis. New York Med. Journ., 1908, lxxxvii, 780.
46. Landis and Norris. Diseases of the chest, 1920, p. 269.
47. Schneider. Bronchitis plastica. Jahrbuch f. Kindh., 1912, lxxv, 34.
48. Hadley. A case of fibrinous or plastic bronchitis. Clinical Jour., Lond., 1917, lxvi, 267.
49. Schnitzler. Wien med. Halle, 1864, v, 44.
50. Vintras. A case of plastic bronchitis with its postmorten appearance. Lancet, Sept. 15, 1900, p. 809.
51. Devillers et Renon. Bronchite pseudomembraneuse aspergillaire primitive. La Presse méd., December, 1899.
52. Finckh. Über actinomykotische fibrinöse Bronchitis; ein neues Symptom der Lungenaktinomykose. Beitrag zur klinischen Chirurgie. Beitrag zur Chir., 1903, Bd. xli, Heft 3,676.

53. Müller. Die Erkrankungen der Bronchien. Plastische oder pseudomembranöse Bronchitis. Die Deutsche Klinik, 1904, Bd. iv, 259.
54. Fraenkel, A. Spezielle Pathologie und Therapie der Lungenkrankheiten, 1904, Chapter IV, 107.
55. Beschorner. Volkmann's Sammlung für innere Med., 1893, No. 73.
56. Rollet. Wien. med. Wchnschr., 1866, Nr. 20, 2nd, 21.

Recently Published

Walker. Two cases of fibrinous bronchitis with review of literature. Am. Jour. Med. Sci., June, 1920, clix, 825.

Putrid Bronchitis

57. Traube. Über putride Bronchitis. Ges. Beitr., Bd. ii, 556.
58. Dittrich. Über Lungenbrand infolge von Bronchialerweiterung. 1850.
59. Rosenstein. Cited by Hoffmann in Die Krankheiten der Bronchien, 1896.
60. Canali. Cited by Hoffmann in Die Krankheiten der Bronchien, 1896.
61. Lumniczer. Wiener Med. Presse, 1888, No. 19.
62. Bernabei. Sulla existenza di una bronchite fetid promaria. Bull. del. Soc. Lancis. degli ospedali di Roma, An. xiii.
63. Hitzig. Beiträge zur Aetiologie der putriden Bronchitis. Virchow's Archiv, 1895, Bd. cxli, 28.
64. Marfan. Maladies des Bronches. In Traité de Médicine, Charcot, Bouchard et Brisseaud, 1893, IV, 287.
65. Fraenkel. Spezielle Pathologie und Therapie der Lungenkrankheiten, 1904.
66. Gerhardt. Die Rheumatoiderkrankungen der Bronchiectatiker. Deutsche Arch. für klin. Med., 1875, Bd. xv, 1.
67. Ephraim. Endobronchiale Therapie. Berl. klin. Wchnschr., 1910, lvii, 1276.

Tracheobronchial Syphilis

68. Conner. Syphilis of the trachea and bronchi; an analysis of 128 cases and report of a case. Am. Jour. Med. Sci., 1903, cxxv, 57.
69. Gerhardt. Über syphilitische Erkrankungen der Luftröhre. Deutsches Arch. für klin. Med., 1866, No. 2, 535.
70. Emanuel. Gumma of the trachea. Brit. Med. Jour., 1912, No. 1, 363.
71. Plicque. La syphilis broncho-pulmonaire, formes et traitement. Jour. de med. et de Chir. prat., 1918, lxxxix, 321.
72. Bouchut et Dujol. Syphilis et dilatation bronchique. Rev. de méd., Par., 1912, xxxii, 585.
73. Denker. Über bronchoscopisch diagnostizierte Tracheobronchial und Lungensyphilis. Deutsch. med. Wchnschr., 1912, xxxviii, Part 1, p. 11.
74. Arrowsmith. Tracheobronchial syphilis. New York Med. Jour., June 24, 1916, p. 1211.
75. Wadsack. Zwei plötzliche Todesfülle infolge syphilitischen Bronchostenose. Charite-Ann., Berlin, 1904, xxix, 211.
76. Kahler. Klinische Beiträge zur Oesophagoskopie und Tracheobronchoskopie. Wien. med. Wchnschr., 1909, lix, 2864, 2898.
77. Pitt. The results of bronchial obstruction. Lancet, 1910, ii, 1674.
78. Hoffmann. Die Krankheiten der Bronchien, 1912.
79. Halle. Fall von gummöser Syphilis der Luftröhre. Berl. klin. Wchnschr., 1911, No. 1, p. 37.
80. Mayer. Sifilis pulmonar, 1916 (Cited by Plicque).
81. Reede. Syphilitic tracheal stenosis. Washington Med. Ann., 1912, 1913, xi, 217.
82. Marcus. Monatschr. f. Ohrenheulk., 1909, xliii, 116. (Cited by Reede.)
83. Vierling. Syphilis der Trachea und der Bronchien. Deutsches Archiv. für klin. Med., 1878, Bd. 21, 325.

Recently Published

Stimson. Syphilis of the trachea and bronchi. A résumé of the diagnostic features with three case reports. Am. Jour. Med. Sci., May, 1921, clxi, No. 5, p. 740.

New Growth of the Bronchi

84. **Pässler.** Uber das primäre carcinom der Lunge. Virchow's Archiv, 1896, cxlv, 191.
85. **Weller.** Primary carcinoma of the large bronchi. Arch. Int. Med., 1913, xi, 314.
86. **Wolf.** Der primäre Lungenkrebs. Fortschritte der Med., 1895, xiii, 765.
87. **Adler.** Primary malignant growths of the lungs and bronchi. 1912.
88. **Jackson.** Endothelioma of the right bronchus removed by preoral bronchoscopy. Am. Jour. Med. Sci., 1917, cliii, 371.
89. **Spiess.** Ein Fall hochgradiger Dypspnöe infolge eines Polypen im rechten bronchus. Münch. med. Wchnschr., 1919, lvii.
90. **Pitt.** The results of bronchial obstruction. Lancet, 1910, ii, 1674.
91. **Ephraim.** Demonstration eines Falles von primären Bronchial tumor. Berl. klin. Wchnschr., 1911, xlviii, 596.
92. **Jex-Blake.** Obstruction of a main bronchus. Clin. Jour., London, April 24, 1914, xliii, No. 17, p. 257.
93. **Fraenkel.** Spezielle Pathologie und Therapie der Lungenkrankheiten. 1904.
94. **Nesbitt.** Clinical notes of a case of intrathoracic tumor. Dublin Jour. Med. Sci., June 1, 1917, cxliii, 353.
95. **Scott and Leist.** Epidermoid cancer of a large bronchus with cavity formation and metastases in the radius. Med. Rec., Sept. 29, 1917, xcii, 541.
96. **Posselt.** Primärer Krebs der Bronchien. Med. Klin., 1911, vii, 1240.
97. **Kirch.** Über die stenosierenden Bronchialgeschwülste mit konsekutiver Bronchiektasenbildung. Centrallbt. f. Path. u. path. Anat., 1917, xxviii, 545.
98. **Knack.** Fall von Bronchiektasenbildung infolge eines Fibroms an der Abgangstelle des unteren Hauptbronchus. Deutsch. med. Wchnschr., 1918, xliv, 1007.
99. **Gerhardt.** Cited by Posselt. Med. Klin., 1911, vii, 1240.
100. **Rokitansky.** Lehrb. d. path. Anat., 1861, Bd. iii.
101. **Siegert.** Über primäre Geschwülste der unteren Luftwege. Virchow's Archiv, 1892, cxxix, 413.
102. **Blecher.** Über die klinische Bedeutung der Bronchialekchondrosen. Mitt. a.d. Grenzgeb. d. Med. u. Chir., 1910, xxi, 837.

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